



HUMAN TOXICOLOGY OF CHEMICAL MIXTURES

**Toxic Consequences Beyond the Impact of
One-Component Product and Environmental Exposures**

HAROLD I. ZELIGER

SECOND EDITION

Human Toxicology of Chemical Mixtures

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Second Edition

Harold I. Zelig



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*To my wife Gail. Your encouragement was the
catalyst that made this happen.*

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Preface to the Second Edition

Since the publication of the first edition of this book in 2008, many new case studies addressing the human toxicology of chemical mixtures have been published. These studies are recognized and incorporated into the text here.

This book has been expanded to include new chapters on nanotoxicology and the toxicology of global warming. New advances in nanotechnology have brought with them new toxicological ramifications for those exposed to nanoparticles. Global warming is impacting people in many ways, including the acceleration of toxic chemical impact on human beings. The implications of these two new areas of toxicology are explored in the new chapters.

A new chapter on children's toxicology has also been added to this edition with the hope that it will bring recognition of the special effects that toxic chemicals have on the world's children. With that in mind, I rededicate this book to my grandchildren, Jessica, Will, Jack, Caroline, Meren, Sadie, and Nate, as well as to yours.

The publication of the first edition has stimulated new research into the human toxicology of mixtures. It is my hope that this book will encourage others to investigate this subject matter.

Harold I. Zeligier
West Charlton, New York
April, 2011

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Preface to the First Edition

I have been a chemical toxicologist for almost 40 years. As such, I have studied and evaluated the toxicities of chemicals and the health effects produced by human exposure to chemical products and environmental chemicals.

This book really began over 30 years ago, when I was confronted with the first of scores of instances where individuals exposed to chemical mixtures subsequently developed symptoms and effects which could not be explained by the known toxicological effects of the individual chemical species. In some instances, these exposures led to effects far in excess of what would be expected from the exposure. In others, effects were noted following exposures to extremely low levels of chemicals and in still others the body organs targeted were not those known to be impacted by the individual chemicals. Stymied, I advised people to look for other causes of the conditions observed. These inquiries, however, led to my research into the area of toxic effects of chemical mixtures and ultimately to this book.

As time progressed, I began to think that the noted effects might in some way be related to the mixtures, but an explanation remained elusive. The breakthrough came while I was simultaneously investigating two separate, unrelated exposures. The first involved the exposures of several people to very low levels of herbicides and their carrier solvents that entered a building with air-conditioning uptake air. The second involved the exposure of an individual to chemicals off-gassing from newly installed carpeting in a home. In both instances, air sampling revealed airborne concentrations of all individual volatile chemicals to be less than 10% of the values known to affect people. Both exposures were to complex mixtures of chemicals and both exposures led to effects unknown for the individual chemical species.

These cases led me to hypothesize that exposures to chemical mixtures could produce “strange” effects. A review of the literature revealed many examples of unexplained health effects on humans following exposures to mixtures. A study of these showed that in every unexplained instance the mixture contained at least one lipophilic (fat soluble) and one hydrophilic (water soluble) chemical. The literature showed that all body tissues have lipophilic barriers surrounding them. This suggested that absorption of lipophilic chemicals should occur more easily than for hydrophilic species. This too was confirmed by the literature and it was then hypothesized that lipophiles facilitate the absorption of admixed hydrophiles. Accordingly, a greater quantity of a hydrophilic species would be absorbed if it were dissolved in a lipophile than would be taken up if the hydrophile were present alone. This, too, was confirmed by the literature. For example, lipophiles are commonly used to facilitate the absorption of hydrophilic pharmaceuticals. It was further hypothesized that greater absorption of hydrophiles might account for the enhanced low-level effects observed. What was not predicted at the time was the observed attack of lipophile/hydrophile mixtures on new target organs.

In multiple cases, however, human exposures to mixtures of lipophiles and hydrophiles showed attacks at organs not known to be targeted by the individual chemicals.

It was found that all bodily systems are affected by some lipophile/hydrophile mixtures. These include the reproductive (infertility), nervous, digestive, skin, musculoskeletal, filtering organ, digestive, respiratory, cardiovascular, immunological, and endocrine systems. A developing fetus or young child (with an incompletely developed immune system) is particularly vulnerable to attack by chemical mixtures.

The sources of lipophilic/hydrophilic chemical exposure include environmental pollution (air, water, and soil contamination), pesticide, herbicide, and fertilizer residues in foods and drinking water, excipients (non-active additives such as colors, flavors, rheological agents, etc.) in foods and pharmaceuticals, industrial chemicals, household chemical products, personal care products, cosmetics, and environmentally synthesized chemicals that are formed from reactions with released chemicals with each other and with naturally present species.

The subject of this book is effects on humans. Animal studies are occasionally cited, but conclusions are drawn primarily from the human experience.

This book is divided into four parts.

Part I contains an introduction, a discussion of chemical toxicology and mechanisms of chemical absorption and of interaction with various body tissues on macro and molecular levels. Also discussed are the body's protective responses to xenobiotic intrusion, including metabolism, immune system, and endocrine system actions.

Part II discusses where the exposures to chemical mixtures come from, including chemical product and environmental sources. Included are air pollution, water pollution, foods, chemicals used in food production, pharmaceutical products, and electromagnetic radiation.

Part III examines the specific effects of mixtures on different body systems and organs and addresses predicting what the effects of uncharacterized mixtures will be. Case studies of specific effects of chemical mixtures on humans are listed and described.

Part IV is devoted to regulatory requirements for toxic chemicals, warnings for chemicals and chemical products, and the need to adjust recommended exposure levels for products containing chemical mixtures. This part also contains suggestions for limiting mixture exposures in the products we use and recommendations for limiting environmental exposures to toxic chemical mixtures.

I wish to acknowledge the encouragement of my children and their spouses, David, Jennifer, Joseph, Christine, Michael, Katie, Laura, and Jeremy, during the research and writing of this book. David and Jennifer, I cannot thank you enough for your critical review. Your scientific focus, intellect, and rigor were invaluable. Jeremy, thank you for your editing and computer skills. These helped immeasurably in the writing of this book.

This book is dedicated to my children and grandchildren as well as to yours and those of everyone else with the hope that they will all live in a healthier world.

Harold I. Zeliger
West Charlton, New York
April, 2008

List of Abbreviations

2,4-D	2,4-Dichlorophenoxyacetic acid
2,4,5-T	2,4,5-Trichlorophenoxyacetic acid
ACD	Allergic contact dermatitis
ACGIH	American Conference of Governmental and Industrial Hygienists
AD	Alzheimer's disease
ADHD	Attention deficit hyperactivity disorder
ALS	Amyotrophic lateral sclerosis
AMI	Acute myocardial infarction
AOT	Air odor threshold
ASD	Autism spectrum disorder
BaP	Benzo[a]pyrene
BET	Brunauer, Emmett, and Teller (surface area)
BFR	Brominated flame retardant
BHA	Butylated hydroxyl anisole
BHT	Butylated hydroxyl toluene
CDC	U.S. Centers for Disease Control and Prevention
CFS	Chronic fatigue syndrome
CNS	Central nervous system
CNT	Carbon nanotube
COPD	Chronic obstructive pulmonary disease
CVS	Cardiovascular system
DBP	Disinfection (or decontamination) by-products
DDE	Dichlorodiphenyldichloroethylene
DDT	Dichlorodiphenyltrichloroethane
DE	Diol-epoxide
DEP	Diesel exhaust particles
DES	Diethyl stilbesterol
DEET	Diethyltoluamide
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
DNAPL	Dense nonaqueous-phase liquid
DOT	U.S. Department of Transportation
EAFUS	Everything added to food in the United States
EDC	Endocrine-disrupting compound
EDTA	Ethylenediaminetetra-acetic acid
ELF	Extremely low frequency
EMR	Electromagnetic radiation
EPA	U.S. Environmental Protection Agency
EPCRA	Emergency Planning and Community Right-To-Know Act of 1986
ET	Electron transfer
ETS	Environmental tobacco smoke
EWG	Environmental working group

FAS	Fetal alcohol syndrome
FDA	U.S. Food and Drug Administration
FD&C	Food Drug and Cosmetic Act
FEMA	Flavor and Extract Manufacturers Association
FHSA	U.S. Federal Hazardous Substances Act
FM	Fibromyalgia
GC/MS	Gas chromatography/mass spectrometry
GRAS	Generally regarded as safe
GSH	Glutathione
H	Hydrophilic compound
HAA	Haloacetic acid
HAN	Haloacetonitrile
HPT	Hypothalamic-pituitary-thyroid (axis)
IARC	International Agency for Research on Cancer
IDLH	Immediately dangerous to life or health
IgE	Immunoglobulin E antibodies
IPA	Isopropyl alcohol
ISW	Industrial waste sites
K_{ow}	Octanol:water partition coefficient
K_p	Permeation coefficient
L	Lipophilic compound
MCL	Maximum contaminant level
MCS	Multiple chemical sensitivity
MIBK	Methyl isobutyl ketone
MND	Motor neuron disease
MOAEL	Minimal-observed-adverse-effect-level
MPCM	Milligrams per cubic meter of air
MS	Multiple sclerosis
MSDS	Material safety data sheet
MSG	Monosodium glutamate
MSW	Municipal solid waste
MWCNT	Multi-wall carbon nanotube
NDD	Neurodegenerative disease
NIOSH	National Institute of Occupational Safety and Health
NOAEL	No-observed-adverse-effect-level
NOEC	No-observed-effect-concentration
NP	Nanoparticle
NSDWR	National secondary drinking water regulations
OA	Occupational asthma
OH	Hydroxyl
OS	Oxidative stress
OSHA	U.S. Occupational Safety and Health Administration
PAH	Polynuclear aromatic hydrocarbon
PB	Pyridostigmine bromide
PBB	Polybrominated biphenyl

PBDE	Polybrominated diphenyl ether
PCB	Polychlorinated biphenyl
PCDD	Polychlorinated dibenzo- <i>p</i> -dioxins
PCDF	Polychlorinated dibenzofurans
PCP	Pentachlorophenol
PD	Parkinson's disease
PEL	Permissible exposure level
PET	Polyethylene terephthalate
PM _{2.5}	Particulate matter less than 2.5 microns
PM ₁₀	Particulate matter less than 10 microns
PMP	Pharmaco-metabonic phenotyping
POP	Persistent organic pollutant
PPB	Parts per billion
PPM	Parts per million
PU	Polyurethane
PVC	Polyvinyl chloride
QAC	Quaternary ammonium compound
RADS	Reactive airways dysfunction syndrome
RF	Radio frequency
RO	Alkoxy
ROO	Peroxy
ROS	Reactive oxygen species
SAB	Spontaneous abortion
SBS	Sick building syndrome
SLE	Systemic lupus erythematosus
SO	Superoxide
SS	Systemic sclerosis
SSc	Scleroderma
STEL	Short-term exposure limit
SWCNT	Single-wall carbon nanotube
TAC	Toxic air contaminant
TCA	Trichloroacetic acid
TCDD	2,3,7,8-Tetrachlorodibenzo- <i>p</i> -dioxin
TCE	Trichloroethylene
THM	Trihalomethane
TRI	Toxic release inventory
TTHM	Total trihalomethanes
TLV	Threshold limit values
TWA	Time-weighted average
UCTD	Undifferentiated connective tissue disease
USDA	U.S. Department of Agriculture
UV	Ultraviolet
VOC	Volatile organic compound
WHO	World Health Organization

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Part I

Introduction to Chemical Toxicology of Mixtures

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1 Introduction

Chapter Outline

References 6

What do Gulf War syndrome, Katrina cough, aerospace syndrome, and epidemic increases in the incidence of autism, attention deficit hyperactivity disorder (ADHD), birth defects, asthma, mailroom illness, spontaneous abortion (SAB), and many cancers have in common? Each of these can be associated with a single causative agent, but each can be associated with environmental exposure to chemical mixtures that do not contain any of the known causative agents.

No doubt that some of the increased numbers of the diagnoses being made for environmentally induced illnesses (such as asthma and ADHD) are due to improved methods of detection and reporting. The huge increases observed, however, cannot be accounted for by increased diligence only.

Many environmentally induced illnesses can be attributed to exposures to single chemical compounds. These have been and continue to be extensively studied and numerous references address them [1, 2]. Table 1.1 lists a few examples of single chemicals and the effects they are known to cause.

Single chemical effects will not be specifically addressed here. Rather, the focus here is on illnesses that ensue following exposures to mixtures of chemicals and that cannot be attributed to any one component of an exposure mixture. A good list summarizing the effects of approximately 2000 single chemicals has been made available by the State of Maine Department of Environmental Protection [3].

Traditionally and historically, toxicologists have addressed the effects of single chemicals. There are thousands of unnatural chemicals in our environment, in the home, and at the work place, and new ones are being constantly added. It is virtually impossible for a person to be exposed to a single chemical. The unborn fetus is exposed to numerous chemicals in utero and babies have been shown to be born with hundreds of synthetic chemicals in their bloodstreams. Nursing babies ingest large numbers of environmental toxins in mother's milk.

As used here, an unnatural chemical is one that is either synthesized by man and unknown in nature (e.g., polychlorinated biphenyls (PCBs), dichlorodiphenyl trichloroethane (DDT), and toluene diisocyanate (TDI)), or known in nature but introduced at concentrations that are much greater than those found in unpolluted environments (e.g., ozone, 1,3-butadiene, and asbestos). We all drink water, breathe air, and eat food that contains hundreds if not thousands of unnatural chemical compounds. Household cleaning and maintenance products, adhesives, paints, disinfectants, and pesticides are

Table 1.1 Single Chemicals and the Effects They Are Known to Cause

Chemical	Effects
Benzene	Leukemia
Bromoform	SAB
DDT	Liver and kidney damage
Dibenzofuran	Skin rashes and pigmentation changes
<i>n</i> -Hexane	Central nervous system (CNS) damage
Methylmercuric chloride	Irreversible brain damage
Trimellitic anhydride	Asthma

just some of the sources of chemical mixtures. Lesser known ones include disposable diapers, marking pens, air fresheners, fragrance products, mattress covers, pharmaceuticals, food flavors and colors, and chemicals inadvertently carried home on clothing of workers. Naturally occurring phenomena such as fires, petroleum seepage, and volcanoes are also sources of chemical mixtures. The interaction of electromagnetic radiation (EMR) with chemicals and the reaction of chemicals with other released or naturally occurring chemicals produce still more mixtures. Exposure to industrial chemicals affects very large numbers of people to wide varieties of single species and chemical mixtures.

Before 1828, it was believed that organic chemicals could only be formed under the influence of the vital force in the bodies of animals and plants. Vital force, also referred to as vital spark, energy and soul, is a tradition in all cultures, including Eastern as well as Western ones. Until 1828, this vitalism, and only it, was believed to be responsible for all factors affecting life, including the synthesis of all organic molecules. It was inconceivable that human beings could create such material. In 1828, Friedrich Wohler accomplished the first synthesis of urea, a naturally occurring component of human urine. Once it was demonstrated that such synthesis was possible, chemists were freed to pursue other such work, and since then, many other naturally occurring compounds have been synthetically prepared. Organic synthesis, however, has not limited itself to duplicating nature. Hundreds of thousands of new, previously unknown to nature, chemicals have been synthesized.

Each new chemical added to our environment potentially creates a vast number of new chemical mixtures with unknown health consequences. The number of compounds is multiplied by chemical reactions of newly released compounds with existing released compounds as well as with naturally occurring species to create yet more toxic molecules. Continual exposure to heat and/or EMR promotes further chemical reactivity and results in the creation of still more toxins. There are no meaningful experiments that can be done because the scope of the problem is undefined. The Earth's flora and fauna, including humans and guinea pigs, are afflicted by these toxicants and often do not understand the causes of these ailments. The results of these multiple exposures often only become evident after people are stricken. Research into

the toxic effects of single chemicals often produces conflicting results when investigators fail to consider the presence of species other than the ones being studied. For example, different effects have been reported following the inhalation of formaldehyde when it was admixed with other chemicals [4].

For single chemical exposures, we know that most individuals are affected by very high concentrations. Individuals who are genetically predisposed and/or have been previously sensitized react to lower concentrations of a chemical. Effects at different concentration levels are, for the most part, known and predictable, enabling proper precautions to be taken [5].

Exposures to mixtures of chemicals produce effects that are, for the most part, unknown and unpredictable. These are:

1. Enhanced effects
2. Low-level reactions
3. Unpredicted points of attack.

An enhanced effect is defined as one where exposure to a chemical mixture produces a reaction at a target organ that is anticipated for one of the chemicals in the mixture, but it is a reaction that is far in excess of that anticipated from the toxicology of the individual chemical species.

A low-level reaction is one where exposure to a mixture of chemicals in which each chemical is present at a concentration far below that known to produce a reaction does indeed impact a target organ that is known to be affected by one of the chemicals.

An unpredicted point of attack reaction occurs when exposure to a mixture of chemicals results in attack on an organ not known to be impacted by any of the individual chemicals in the mixture.

The human body is a complex mixture of chemicals. We have evolved and adapted over time to contacting, eating, drinking, and breathing the chemicals naturally present in our environment. We are not always prepared for the assault of “unknown” synthetic chemicals on our bodies. The introduction of a foreign chemical species (xenobiotic) challenges the body’s natural defense mechanisms to defend against an unknown challenger. The body responds by trying to metabolize the invader so that it can be eliminated, and/or fights it with its immune system. Most people are thus able to defend against foreign chemical species. Mixtures, however, present a special challenge to the body’s natural defenses. Often, one part of a mixture attacks a particular organ while a second species attacks a component of the defense mechanism trying to defend the body. This will be explored in more detail in later chapters.

Our inability to defend against new chemicals and mixtures often results in epidemics of disease. For example, asthma, autism, infertility, and many cancers affect different parts of the body and seemingly have different etiologies. All, however, can be related to a combination of genetic predisposition and environmental exposure to chemicals. All are less prevalent where chemical exposures are lower; for example, in rural areas. All have known single chemical exposure causes and all can also be related to low-level exposure to chemical mixtures. The toxic effects of chemical mixtures will be explored in the chapters that follow.

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2 Health Effects of Exposures to Chemical Mixtures

Chapter Outline

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2.1 Traditional Toxicology

Traditionally, toxicologists have addressed the effects of chemical mixtures as being additive, antagonistic, potentiated, or synergistic [1]. To these, sequential effects are also added here.

2.1.1 Additivity

Additive effects occur when two or more substances with the same toxicity (i.e., attack the same organ) are present together. The total or additive effect is the sum of the individual effects. Additive effects are observed when mixtures consist of species that are similar, that is, act identically on a target organ. Additive effects may be observed, for example, when a mixture of two compounds, each below the no-observed-exposure-level (NOEL), produces a predicted toxic effect when the sum of their concentrations is greater than the threshold level for toxic action.

Examples of chemical mixtures that produce additive effects are:

1. *n*-Hexane and methyl-*n*-butyl ketone (peripheral neuropathy) [2].
2. Trichloroethylene (TCE) and tetrachloroethylene (liver and kidney toxins) [3].
3. Toluene and xylene (brain function loss) [4].

2.1.2 Antagonism

Antagonism occurs when two chemicals interfere with each other's effect. The result is a reduction in the effect predicted for the individual species. Antagonistic mixtures need not be structurally similar. One species may stimulate the metabolism of a second one or somehow interfere with its sorption. Antagonism can be considered the antithesis of synergism (discussed later).

Examples of chemical mixtures that produce antagonisms and their effects are:

1. DDT and parathion (DDT induces and parathion inhibits enzymatic activity) [5].
2. Oxygen and carbon monoxide (oxygen competes with CO for receptor sites) [6].
3. Toluene and benzene (toluene inhibits benzene metabolism and reduces its toxicity) [7].

2.1.3 Potentiation

A potentiated effect is observed when the effect of a chemical is enhanced by the presence of one or more other compounds that are only slightly active. One compound can potentiate a second one toxicologically, for example, by producing the same metabolites in the body.

Examples of chemicals mixtures that produce potentiated effects are:

1. Organophosphorothiolate esters potentiate malathion (CNS) [8].
2. Isopropanol potentiates carbon tetrachloride (liver) [9].
3. Methyl ethyl ketone (MEK) potentiates *n*-hexane (CNS and peripheral nervous system) [10].

2.1.4 Synergism

Synergism is observed when the effect of exposure to a mixture is much greater than or different from that expected from an additive effect. In such instances, exposures to mixtures of chemicals that are substantially different from each other induce responses not predicted by the known toxicology of the individual chemical species. When synergistic effects are observed, one of the chemicals of the mixture changes the body's response in a qualitative or a quantitative way. A quantitative response is one that is much greater than would be observed for an additive effect. A qualitative effect results in attack at a different target organ that is not predicted.

Examples of chemical mixtures that produce synergism and their effects are:

1. Nitrate and aldicarb (immune, endocrine, and nervous systems) [11].
2. Carbon disulfide and carbon tetrachloride (nervous system) [12].
3. Cigarette tar and nitric oxide (carcinogenic) [13].

2.1.5 Sequential Effects

Sequential effects arise when one chemical is absorbed first and the second one is absorbed at a finite, but important time, thereafter resulting in an effect not observed from exposure to either one of the single chemicals. Examples that demonstrate this effect are:

1. The administering of ethanol or acetone prior to administering acetaminophen results in a marked increase in the hepatotoxicity of acetaminophen (due to enzyme induction by ethanol) [14].

2. Pretreatment with diethyl maleate increases toxicity of bromobenzene (due to depletion of glutathione by diethyl maleate) [15].
3. Individual with hepatic injury, such as alcohol-induced cirrhosis, experiences greater hepatotoxic effects than those not so previously injured [16].

The toxic mixture examples just presented here are only a small fraction of those that will be fully discussed and referenced in Part III of this book.

2.2 Unexplained Effects of Mixtures

As noted in Chapter 1, exposure to chemical mixtures can produce enhanced effects, low-level reactions, and unpredicted points of attack. The toxicological literature reported these, but until recently was at a loss to offer an explanation. The following published studies are illustrative of how toxicologists viewed the unexpected effects of exposures to mixtures prior to 2003.

Alessio [17] reviewed the literature and reported on the exposure of workers to multiple solvents in the workplace. His study showed that exposures to some solvent mixtures resulted in the inhibition of the metabolism of the solvents, while exposures to other solvent mixtures enhanced the metabolism of the solvents. No explanations of the effects noted were offered.

Feron et al. [18] studied the effects of mixtures administered at the “no-observed-adverse-effect-level” (NOAEL) and the “minimum-observed-adverse-effect-level” (MOAEL). Evidence of an increased hazard was found when combinations of chemicals were administered at the NOAEL of each of the components, despite the fact that exposures to the individual chemicals had no adverse effects. When mixtures were administered at the MOAEL levels of the individual components some severe adverse effects were noted.

Alexandersson et al. [19] studied the effects of exposure of carpenters to formaldehyde, terpenes, and dust particles. The mean formaldehyde levels were far below the threshold value. The terpene levels were very low and frequently undetectable and dust levels were about one-tenth of the threshold levels. At the concentration levels recorded, no respiratory effects would be expected, yet dyspnea (shortness of breath), nose and throat irritation, chest tightness, and productive cough were observed. These results were reported without explanation.

Formaldehyde exposure is not known to cause neurobehavioral symptoms or disturbed mental or neurologic function. Kilburn et al. [20], however, found that exposure by hospital histology technicians to formaldehyde, xylene, and toluene produced such effects. No attempt was made to explain these results.

A study of rubber workers exposed to a mixture of resorcinol, formaldehyde, and ammonia revealed that these workers suffered acute drops in lung function and other respiratory symptoms over a work shift. The levels of exposure of the chemicals were low. The researchers concluded that the cause for the observed effects was unknown [21].

Brooks et al. [22] reported several instances of reactive airways dysfunction syndrome (RADS) following exposures to mixtures of chemicals, each of which

contained no compounds known to cause respiratory sensitization. In the first instance, a store clerk was stricken with RADS following application of a floor sealant containing a mixture of aliphatic and aromatic hydrocarbons and epichlorohydrin. In the second instance, two painters were stricken after spray painting primer in an apartment. The primer contained a mixture consisting of ammonia, aluminum chlorohydrin, and other unidentified additives. In another case, a woman was stricken within 15 min of the application of a fumigant containing polyoxyethylated vegetable oil, dipropylene glycol, a turpine hydrocarbon, sodium nitrate, an unsaturated aldehyde, and isobornyl acetate. No attempt was made to account for the observed effects.

Lee et al. [23] reported on the prevalence of pulmonary and upper respiratory tract symptoms experienced by pressmen exposed to low levels of aliphatic hydrocarbons, limonene, glycol ethers, isopropyl alcohol, and mineral oil. The airborne levels of these solvents were below the permissible exposure limits. No explanation was offered to account for the observed results.

Waterborne paints are generally low in volatile organic compounds (VOCs) and not thought of as being particularly dangerous. Typical formulations include glycol ethers, esters, glycols, formaldehyde, and amines. Hansen et al. [24] investigated the waterborne paints used in Denmark and their effects on painters. They reported that mucous membrane irritation was observed in these painters even though the airborne concentrations of the volatiles were, for the most part, below the known irritation levels for the single chemicals. The researchers concluded that irritation due to the combined action of the chemicals cannot be excluded but offered no explanation for this conclusion.

Dossing and Ranek [25] reported on liver damage in chemical workers exposed to low levels of carbon disulfide, isopropanol, toluene, and other chemicals in trace quantities. The researchers suggested that the liver injury was caused by the combined action of organic solvents and compared it to the known synergistic effect of isopropanol on the hepatotoxicity of carbon tetrachloride [26].

2.3 Lipophiles and Hydrophiles

In 2003, Zeliger reported that in all the cases of these unusual effects of mixtures cited in the literature, the mixtures contained at least one lipophilic and one hydrophilic chemical. A lipophilic chemical is one that exhibits preferential solubility in relatively less polar species. A hydrophilic chemical is one that exhibits preferential solubility in relatively more polar species. Lipophiles promote the permeation of hydrophiles through mucous membranes resulting in the absorption of greater quantities of hydrophilic species than would be absorbed if the lipophile were not present. Once absorbed, the mixtures of chemicals may affect the body in ways not anticipated from the actions of single chemicals alone. It was found that the effects of the absorbed mixtures may be acute or chronic [27].

Since 2003, toxicologists have begun to address the hazards posed by exposures to chemical mixtures and to the effects of low-level exposures by humans to mixtures [30, 31].

2.4 Octanol:Water Partition Coefficients

The relative differences in lipophilicity and hydrophilicity are reflected by the *n*-octanol:water partition coefficients of the chemicals, K_{ow} [28]. K_{ow} is indicative of the relative lipophilic character of a given chemical. It is defined as the ratio of that quantity of a chemical dissolved in the *n*-octanol phase to that dissolved in the water phase of an octanol–water mixture. Because it is a ratio, K_{ow} has no units and is expressed as a logarithm of that ratio due to the wide range of values for different compounds:

$$\text{Log } K_{ow} = \log [(\text{solute in } n\text{-octanol})/(\text{solute in water})]$$

A K_{ow} value of 3.0 for a compound means that the compound is 1000 times more soluble in *n*-octanol than in water.

n-Octanol was chosen as the solvent for this ratio because it mimics the lipids found in living tissue and thus provides a basis for providing information about the absorption of a compound into living tissue.

The K_{ow} values of most compounds range from less than -1.0 to greater than 6.0 . Chemicals with K_{ow} values greater than 2.0 are regarded as lipophiles and those with K_{ow} values less than 2.0 are considered hydrophiles. Table 2.1 lists some common

Table 2.1 Octanol:Water Partition Coefficients (K_{ow}) for Some Common Chemicals

Chemical	K_{ow}	Chemical	K_{ow}
Acetaldehyde	−0.34	Ethyl acetate	0.73
Acetic acid	−0.17	Ethyl benzene	3.15
Acetone	−0.24	Ethylene glycol	−1.36
Aldicarb	1.13	Ethylene oxide	−0.30
Ammonia	−1.38	Formaldehyde	0.35
Amyl acetate	2.26 ^a	<i>n</i> -Heptane	4.66
Atrazine	2.61	<i>n</i> -Hexane	3.90
Benzene	2.13	Hydrofluoric acid	0.23 ^a
Benzophenone	3.18	Isobutene	2.76
1,3-Butadiene	1.99	Methanol	−0.77
<i>n</i> -Butanol	0.88	Methylene chloride	1.25
2-Butoxyethanol	0.83	Methyl ethyl ketone	0.29
Butylated hydroxytoluene (BHT)	5.10	Methyl isobutyl ketone	1.19
Carbon disulfide	1.94	Naphthalene	3.30
Chloroform	1.97	Nitric acid	0.21 ^a
Cyclohexane	3.44	<i>i</i> -Propanol	0.05
<i>n</i> -Decane	5.01	<i>n</i> -Propyl acetate	1.24
Dimethylformamide	−1.01	Styrene	2.95
2,4-Dichlorophenoxyacetic acid (2,4-D)	0.65	Tetrachloroethylene	3.40
Epichlorohydrin	0.45	Toluene	2.73
Ethanol	−0.31	1,1,1-Trichloroethane	2.49
2-Ethoxyethylacetate	0.59 ^a	Vinyl acetate	0.73
		Vinyl chloride (VC)	1.62 ^a
		Xylene	3.15

^aCalculated values.

chemicals and their K_{ow} values. The K_{ow} values reported here as well as elsewhere in this book are experimental values, when available. Otherwise, calculated values were used [28, 29].

2.5 Summary

Traditional toxicology addresses the toxic effects of single chemicals and even some of the mixture effects (additivity, potentiation, and synergism) well, but it is unable to account for some observed effects of chemical mixtures. These unexplained effects often ensue when exposures are to mixtures of lipophilic and hydrophilic chemicals. Octanol:water partition coefficients serve to predict the lipophilic or hydrophilic nature of chemical compounds.

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3 Absorption of Chemical Mixtures

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3.1 Introduction

Chemicals can be absorbed in the human body via inhalation, ingestion, and dermal and eye contact. A single chemical can enter the body through more than one route. Chloroform is an example of such a species. Chloroform is found in contaminated groundwater and also in many municipal water supplies where it results from the chlorination of drinking water that contains high levels of organic matter. People living in homes where chloroform contaminated drinking water is supplied absorb the chemical via ingestion when drinking it, via inhalation when it is vaporized during cooking or showering, and via dermal contact when washing or bathing.

Most body tissues are protected by lipophilic barriers that serve as the body's primary protection against absorption of chemicals [1]. It is well established that lipophilic chemicals can penetrate lipophilic barriers (including mucous membranes) much more readily than can hydrophilic chemicals by passively diffusing across lipid-rich cell membranes [2–4]. The lipid-rich mucous membranes also serve as barriers to the absorption of hydrophilic species. Lipophilic chemicals, however, promote the permeation of hydrophilic chemicals that are dissolved in the lipophiles. Lipophiles are routinely used, for example, in drug-delivery systems (see Section 3.3).

3.2 Permeability of Mucous Membranes and Octanol:Water Partition Coefficients

The relationship between lipophilic membrane permeability and K_{ow} is well described in the literature. Kitagawa, Li, and Sato [5] reported that permeability coefficients

Table 3.1 Relationship of Permeability Coefficients (K_p) and Octanol:Water Partition Coefficients (K_{ow}) for Parabens [5]

Paraben	K_{ow}	K_p
Methyl	1.66	6.51
Ethyl	2.19	32.67
Propyl	2.71	66.26
Butyl	3.24	92.17

Table 3.2 Permeability Constants (K_p) [9] and Octanol:Water Partition Coefficients (K_{ow}) for a Homologous Series of Alcohols

Alcohol	K_p	K_{ow}
Methanol	1.0	-0.77
Ethanol	1.2	-0.31
Propanol	1.4	0.25
Butanol	2.5	0.88
Pentanol	6.0	1.51
Hexanol	13.0	2.03
Heptanol	32	2.62
Octanol	52	3.00

across excised skin increased directly with K_{ow} for a homologous series of parabens. As can be seen from the data in Table 3.1, greater permeability is directly related to greater lipophilicity (higher K_{ow}).

Potts and Guy [3] concluded that lipid properties of chemicals account for permeability through the stratum corneum of the skin and that that permeability is a function of the K_{ow} of a compound. Bowman and Maibach [6] showed that the percutaneous absorption of the hydrophilic butanol increased when simultaneously exposed with a lipophilic surfactant.

Siegel [7, 8] studied the permeability of the oral mucosa. He found that in a homologous series, an increase in lipid solubility resulted in an increased permeability of the oral mucosa. His permeation constants correlate exactly with K_{ow} values.

Scheuplein and Ross [9] reported that skin permeability was increased by treatment with nonpolar solvents. Their data show that permeability constants for a homologous series of alcohols are a function of carbon number, a relationship that corresponds exactly to increasing K_{ow} . These data are shown in Table 3.2.

The work of Geyer et al. shows a direct relationship between the increasing K_{ow} values and the bioaccumulation potential of organic chemicals [19]. This relationship was shown to hold for a wide variety of organic compounds and to be independent of functionality of the species. There is a quantitative relationship between K_{ow} and diffusion limitation of exchange between adipose and blood [19].

Witte, Jacobi, and Juhl-Strauss [11] determined that subtoxic concentrations of membrane-damaging compounds enhanced the cytotoxicity of hydrophilic xenobiotics

Table 3.3 K_{ow} and NOEC Values for Various Compounds Combined with 2,4-D

Compound	K_{ow}	NOEC (mM)
Dimethyl sulfoxide	-1.35	1380
Ethanol	-0.32	129
Dichloroacetic acid	0.94	10.0
Nitrilotriacetic acid	1.06	7.6
4-Chloroaniline	1.83	5.9
Picloram	2.27	5.0
4-Chlorophenol	2.36	1.7
Chloroflurenol	3.22	1.5
2,4,6-Trichlorophenol	3.70	2.5
Tributylamine	4.60	8.7
Pentachlorophenol (PCP)	4.89	0.10
Dicofol	5.02	0.15

(foreign compounds). The data reported show a linear relationship between the logarithm of the no-observed-effect-concentration (NOEC) and K_{ow} values; the higher the K_{ow} , the lower the log NOEC and the greater the toxicity of the mixture. The data in Table 3.3 show K_{ow} and NOEC in millimoles (mM) for 2,4-dichlorophenoxyacetic acid (2,4-D). The sole deviant from the relationship, tributylamine, is explained by its extremely low membrane-damaging properties relative to its lipophilicity.

The data in Table 3.3 are remarkable in that, despite the fact that the chemical and toxicological properties of the compounds studied vary widely, the effects of these chemicals on the toxicity of 2,4-D are predicted by K_{ow} values. The authors hypothesized that combinations of lipophilic and hydrophilic compounds would show synergistic effects resulting from membrane damage by lipophilic species and increased uptake of hydrophilic species.

3.3 Absorption Enhancers

Most pharmaceuticals are hydrophilic and do not penetrate epithelial barriers at clinically useful rates. It has long been known that lipophilic molecules serve as permeability enhancers for such drugs [12, 13]. This is consistent with the data reported earlier; that is, that lipophilic species facilitate the absorption of hydrophilic ones.

The literature contains numerous examples of permeability enhancement by lipophilic species. Two of these are presented here.

Kitagawa, Li, and Sato [5] reported that the addition of 1% L-menthol increased the permeability coefficient of methyl paraben about 16-fold. Manganaro and Wertz [12] reported on the use of oleic acid to facilitate the permeability of propanolol, a widely used beta-blocking agent. In concentrations of 1–10%, the use of oleic acid resulted in a three- to fourfold increase in the absorption of the drug.

Table 3.4 K_{ow} and K_p for Organic Compounds Dissolved in Aqueous Solutions [18]

Chemical	K_{ow}	K_p
Water	-1.38	0.00020
Methanol	-0.70	0.00050
Ethanol	-0.30	0.00080
Propanol	0.34	0.0012
Butanol	0.88	0.0025
Pentanol	1.40	0.0060
Hexanol	2.03	0.013
Heptanol	2.41	0.032
Octanol	3.15	0.052
Nonanol	3.62	0.060
Decanol	4.00	0.080
Resorcinol	0.78	0.00024
Phenol	1.46	0.00822
<i>p</i> -Cresol	1.92	0.0175
<i>o</i> -Cresol	2.00	0.0157
<i>m</i> -Cresol	2.01	0.0152
<i>o</i> -Chlorophenol	2.19	0.033
<i>p</i> -Chlorophenol	2.39	0.0363
β -naphthol	2.80	0.0279
Thymol	3.34	0.0528
2,4,6-Trichlorophenol	3.69	0.0594

3.4 Absorption of Organic Molecules from Aqueous Solutions

The discussion to this point has been limited to absorption of pure compounds and mixtures. In the real world, however, people are exposed to numerous chemicals that are dissolved in water. The correlation between increasing K_{ow} and absorption holds for aqueous solutions as well as it does for the pure compounds. Several studies have been carried out to measure and predict skin permeation rates [14–17]. Though molecular weight and size certainly are factors in determining permeation rates, octanol:water partition coefficient values prove to be valuable predictors of absorption rates. The relationship between K_{ow} values and observed permeation coefficients (K_p) for organic compounds dissolved in water can be readily seen from the data in Table 3.4 that were reported by Wilschut et al. [18]. Two sets of compounds are shown. The first is a homologous series of alcohols and the second is a listing of phenol and its derivatives.

3.5 Summary

The majority of xenobiotics that are absorbed by the body are lipophilic and can permeate through body membranes. The uptake of hydrophilic species by the body,

however, be they solvents, pharmaceuticals, or other chemicals, is facilitated by the presence of lipophilic species. K_{ow} values predict which chemicals are hydrophiles and which are lipophiles. Exposures to chemical mixtures of lipophiles and hydrophiles will result in the absorption of greater quantities of hydrophiles than would be taken up if these species were present alone.

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4 Chemical Toxicology

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4.1 Introduction

Substances that adversely affect those organisms that are exposed to them are poisons. Toxicology is the science that is devoted to the study of the effects of poisons on living organisms. This book will consider only chemical toxicology; that is, the effects of chemical poisons. The effects of biological poisons, bacteria, viruses, and fungi will not be addressed here.

Molecular biology has progressed to the point where many of the toxicological mechanisms are now understood on a molecular level. This chapter surveys these mechanisms. The reader is directed to texts on the subject for a comprehensive treatment of the area [1, 2].

4.2 Toxicology

The toxic effects of chemical poisons are dose related. At low enough doses, organisms can be exposed to even the most toxic of substances without suffering a deleterious impact. Toxicology addresses the effects of exposures to doses ranging from the minimum quantities required for impact through levels that cause instant death.

Toxicological data are presented in a number of different ways. These data and their commonly used abbreviations are listed as follows:

- NOEL No-observed-effect-level. This is the highest level at which no toxicological effects are noted. This level is often presented as NOAEL—no-observed-adverse-effect-level.
- NOEC No-observed-effect-concentration. This datum is identical to NOEL.
- MOEL Minimum-observed-effect-level. This is the lowest concentration at which adverse effects are noted. This level is often presented as MOAEL—minimum-observed-adverse-effect-level.
- PEL Permissible exposure level. PEL data are those established by the U.S. Occupational Safety and Health Administration (OSHA) for inhalation exposures in the workplace.
- TWA Time-weighted average. TWA data are for exposures in the workplace. These are set by the National Institute of Occupational Safety and Health (NIOSH) for inhalation of airborne contaminants.
- TLV Threshold limit values. These are similar to PEL data, but are set by the American Conference of Governmental and Industrial Hygienists (ACGIH). TLV data tend to be more conservative; that is, lower levels than PEL data.
- STEL Short-term exposure limit. Recommended inhalation exposure level for exposures up to 20 min.
- IDLH Immediately dangerous to life or health. Airborne concentrations at which even momentary exposure can kill or seriously injure.
- MCL Maximum contaminant level. This value is generally given for contaminants dissolved in drinking water.

Inhalation data, PEL, TWA, TLV, STEL, and IDLH data are generally presented in units of parts per million (ppm), part per billion (ppb), or milligrams per cubic

meter of air (mpcm). MCL data are generally presented in milligrams or micrograms per liter of water.

The exposure limits listed for individual chemicals are arrived at via a combination of scientific and political considerations, with different groups looking at the same data arriving at different exposure limit recommendations. As an example of this let us consider methyl isobutyl ketone (MIBK). MIBK targets the eyes, skin, respiratory system, CNS, liver, and kidneys. The OSHA TWA for MIBK is 100 ppm while NIOSH and ACGIH recommend a TWA of 50 ppm. Such differences can arise from a difference of scientific opinion and/or the vested interests of those who manufacture and sell a particular chemical. The data, nevertheless, are a reflection of the body's ability to protect itself against the hazards posed by a particular xenobiotic. A higher exposure level value indicates a reduced danger. In the MIBK example, TWA of 50 ppm indicates a greater hazard for this chemical than a value of 100 ppm.

4.3 Molecular Toxicology

Molecular biology has progressed to the point where many bodily functions and their impact by xenobiotics are now understood at a molecular level. This progress has enabled toxicologists to ascribe responsibility for detrimental impacts to specific chemical species and/or their metabolites. These are examined in this section.

When a xenobiotic acts upon an organism, a sequence of events occurs. These are:

- Exposure
- Absorption
- Distribution
- Metabolism
- Toxic activity
- Immune system response
- Endocrine system response
- Excretion.

These are considered individually later.

4.4 Exposure

The first step in the poisoning of an organism is its exposure to a toxic substance. In order to be exposed, the organism and the poison must come to occupy the same space. In the human experience this means that a person must inhabit an environment in which he or she inhales or traverses air, uses water to drink, bathe or cook with, or eats food that contains xenobiotics. In the world we live in today, it is virtually impossible for a person to live in an environment that is toxicant-free. Our challenge in trying to evaluate the impact of xenobiotics is to try to separate out the effects of the substances being evaluated from the "background" contamination.

Since this is essentially impossible to do, we must appreciate that almost all exposures to toxic chemicals are to mixtures and not single compounds.

4.5 Absorption

Chemicals are taken up by the body through cell membranes on the skin, in the eye, in the respiratory tract, and in the digestive tract. The discussion here is limited to those chemicals that traverse membranes biochemically. Corrosive chemicals that destroy tissue, such as strong mineral acids and highly concentrated alkaline compounds, are excluded from consideration here.

As has been noted in Chapter 3, essentially all body tissues are surrounded and protected by lipophilic membranes. Accordingly, absorption into the human body requires mucous membrane breaching. All low-molecular-weight lipophilic chemicals, those with K_{ow} values of 2.00 or more, easily penetrate mucous membranes. High-molecular-weight molecules do not penetrate easily due to their bulk. As also previously addressed, hydrophilic chemicals, those with K_{ow} values of less than 2.00, do not appreciably penetrate through mucous membranes but can be carried through such membranes when dissolved in lipophiles.

At times, such as in drug administration, lipophiles are deliberately added to hydrophilic pharmaceuticals to facilitate absorption. Most often, however, the administering of combinations of lipophilic and hydrophilic chemicals is unintentional and leads to enhanced toxic effects on the body. Once taken up by the body, the distribution, metabolism, immune system response, endocrine system response, and effects on a wide variety of organs in the body are impacted by the mixtures and their metabolites.

4.6 Distribution

Toxic chemicals are carried throughout the body by the blood. These chemicals bond to blood proteins, most notably lipoproteins composed of triglycerides, esterified cholesterol, and phospholipids. The bonding between the toxic chemicals and the blood proteins takes many forms, depending upon the chemistry of the compound transported. The bonding types include ionic, covalent, van der Waals, and hydrogen bonding. In the case of mixtures, the distribution of foreign chemicals can result in one species being transported to one location while a second species is bonded differently to blood proteins and delivered to a second completely different location.

It is important to note that transport of toxic species is not limited to those molecules that are taken up. Metabolism (see Section 4.7) can take place at the point of uptake, and the metabolites as well as the unmetabolized species are transported and distributed throughout the body to places where they ultimately act. Or, alternatively, the absorbed xenobiotic can be transported to another organ where it is metabolized. It can act at that point or be subsequently carried to the place where it acts.

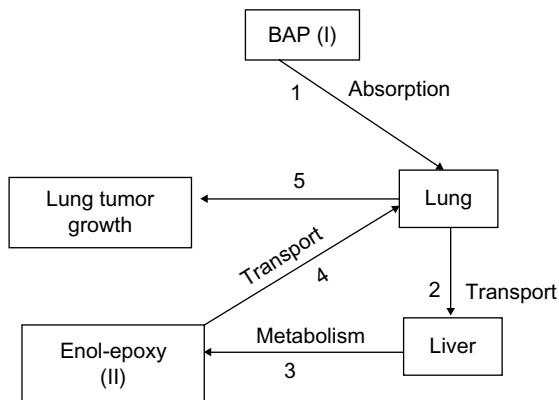


Figure 4.1 Movement and action of benzo[a]pyrene (I) and its diol-epoxy metabolite (II).

An example of how transport impacts effects on the body can be seen from a consideration of benzo[a]pyrene (BaP). BaP is a polynuclear aromatic hydrocarbon (PAH) that is a component of petroleum and cigarette smoke. It is an established lung carcinogen, but it is BaP's diol-epoxide (DE) metabolite that is the actual tumerogen. The path from absorption to tumor production is a five-step process involving two transport steps. The five steps that are depicted in Figure 4.1 are:

1. BaP (I) is absorbed in the lung.
2. BaP is transported to the liver.
3. In the liver, BaP is metabolized to a DE derivative (II).
4. The metabolite is transported back to the lung.
5. DE acts in the lung as the ultimate tumerogen.

In the case of absorption of mixtures, one or more of the chemicals may be metabolized at the uptake point producing multiple species for distribution. Even the absorption of small numbers of toxic chemicals can thereby result in the presence of numerous toxic species being distributed to multiple body sites.

4.7 Metabolism

Chemicals that are absorbed into the body are metabolized by a wide range of enzymes to more water-soluble forms that can be eliminated from the body. Metabolism generally takes place in two phases. In Phase I, a polar functional group is introduced into the molecule. In Phase II, the functional group introduced is combined with an endogenous compound to form a water-soluble species that can be eliminated from the body.

Phase I reactions include oxidation, reduction, hydrolysis, epoxide hydration, and dehydrohalogenation reactions. The cytochrome P450 oxygenase system (CYP450) is the most important one in the metabolism of foreign chemicals. These enzymes that oxidize xenobiotics are widely distributed in the body. They are found in high

Table 4.1 Phase I Enzymes**Oxidation**

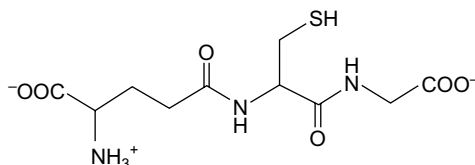
- CYP450 monooxygenase
- Flavin-containing mono-oxygenase system
- Alcohol dehydrogenase and aldehyde dehydrogenase
- Monoamine oxidase
- Co-oxidation peroxides

Reduction

- NADPH-CYP450 reductase
- Reduced (ferrous) CYP450

Hydrolysis

- Esterases
- Amidases
- Epoxide hydrolase

**Figure 4.2** GSH structure.

concentrations in the liver, kidney, lung, nasal passages and intestinal tract, and in lesser, but significant, concentrations in most other tissues. CYP450 enzymes introduce reactive hydroxyl groups into aliphatic hydrocarbons, aromatic rings, and other unreactive compounds. CYP450 enzymes oxidize many chemicals, including benzene, BaP, 2-naphthylamine, and acetaminophen. Other enzymes also play prominent roles in xenobiotic metabolism (see Table 4.1).

Phase II reactions are conjugation reactions in which glutathione (GSH; Figure 4.2) and related compounds are conjugated with the reactive group introduced in Phase I for increased water solubility and facile elimination. Conjugation reactions include sulfation, acetylation, methylation, glucosidation, glucuronidation, GSH conjugation, amino acid conjugation, and lipophilic conjugation. Table 4.2 lists the major Phase II enzymes.

GSH, Figure 4.2, is perhaps the most important of the Phase II enzymes in the biotransformation and elimination of xenobiotics. It also defends cells against oxidative stress (OS) (see Section 4.9).

Toxic chemicals that attack or interfere with Phase I or II enzymes can either enhance or reduce the toxicities of other chemicals by retarding or accelerating the metabolism and removal of these other chemicals. The following scenarios illustrate this point.

Table 4.2 Major Phase II Enzyme Systems

Glutathione <i>S</i> -transferases
UDP-glucuron(oxyl)transferases
<i>N</i> -Acetyltransferases
Amino acid <i>N</i> -acyl transferases
Sulfotransferases

1. Chemical I, with little or no toxicity, is metabolized to a highly toxic species. A second chemical that induces the metabolizing enzymes would increase the toxicity of chemical I. A second chemical that retards the enzymes that metabolize chemical I would reduce the toxicity of chemical I.
2. Chemical II, a highly toxic chemical, is detoxified when metabolized. A second chemical that enhances metabolism would reduce the toxicity of II. A second chemical that inhibits metabolic activity would increase the toxicity of II.

Examples of enzyme-inducing chemicals are ethanol, acetone, phthalates, PCBs, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), DDT, 2,4-D, and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) (the last two are the components of Agent Orange).

Examples of enzyme-inhibiting chemicals are disulfiram, metyrapone, diethyl maleate, and 1-aminobenzotriazole.

Not all xenobiotic metabolites are readily eliminated from the body. Some of the conjugates produced in Phase II metabolism have lipophilic character and are included in the biosynthesis of body lipids. These are retained in the body and have delayed toxic effects.

Though the toxicity of xenobiotics is generally decreased by metabolism, some xenobiotic metabolites are more toxic than their parent compounds. As noted earlier, the metabolite of BaP is the lung carcinogen. Similarly, it is the metabolite of 1-naphthylamine and not the parent compound that is a bladder carcinogen.

4.8 Factors Affecting Metabolism of Xenobiotics

Many factors affect the metabolism of xenobiotics. These include:

- Age
- Gender
- Pregnancy
- Disease
- Hormones
- Cycles
- Enzyme induction or inhibition
- Diet and nutrition
- Dose and timing
- Genetics.

4.8.1 Age

The developing fetus and neonate have little or no ability to metabolize xenobiotics. Though the fetus is protected by its mother in utero, it is particularly vulnerable to assault by xenobiotics. The effects of xenobiotics on the developing fetus will be discussed in some detail in a subsequent chapters 19 and 24.

The ability to metabolize xenobiotics develops rapidly after birth, peaks in early adulthood, and ebbs with age. The very young and the aged are impacted to a far greater degree by absorbed chemicals than young adults.

4.8.2 Gender

Animal studies have demonstrated that some xenobiotics have a greater impact on males, while others more severely affect females. In some instances testosterone and in others estrogens exert stimulating effects on the action of enzymes that metabolize xenobiotics. This has been little studied in human, but it is worth considering when one is confronted with the greater sensitivity of one gender to particular foreign chemicals.

4.8.3 Pregnancy

Pregnant females have a reduced ability to metabolize xenobiotics. This is so because of the reduced activity of a large number of maternal enzymes during pregnancy. Accordingly, it is particularly important that pregnant women should avoid exposures to toxic chemicals as much as possible.

4.8.4 Disease

Disease can be a major factor in reducing the body's ability to rid itself of xenobiotics. Liver, kidney, and cardiovascular disease can impair the ability to metabolize, transport, and eliminate toxic chemicals.

Infection and inflammation of tissues have also been shown to alter the activity of CYP450 enzymes in the liver, kidney, and brain of humans. Such reduced activity affects Phase I metabolism of xenobiotics and results in increased toxic effects. In the case of administration of drugs to combat an infection, these effects can result in toxic side effects from the treatment of the infection. Immune system responses to infection can have a negative effect on CYP450 enzyme metabolism of xenobiotics (see Section 4.12).

4.8.5 Hormones

The hormones produced by the endocrine system play a large role in the metabolism of xenobiotics by controlling the production of metabolizing enzymes. Pituitary hormones, growth hormones, thyroid hormones, adrenal catecholamines, and steroid hormones affect CYP450 production and activity. Accordingly, any foreign chemical that impacts the organs of the endocrine system affects xenobiotic metabolism.

4.8.6 Cycles

Xenobiotic metabolism has been observed to vary with circadian and seasonal cycles in wild animals. These correspond to variations in Phase I and Phase II enzyme production during breeding cycles. In humans, shift workers have been found to have increased rates of heart disease and metabolic illness. This has been attributed to the finding that one-fifth of liver enzymes shows circadian rhythms.

4.8.7 Enzyme Induction or Inhibition

Xenobiotics can serve to induce or inhibit enzymes that are metabolically important. This effect is particularly important when considering the effects of toxic chemical mixtures. Chemicals that are non-toxic or mildly toxic can serve to potentiate or synergize the toxicity of other compounds by inducing or inhibiting the detoxifying enzymes.

4.8.8 Induction

Enzyme induction is an increase in enzyme activity as a result of increased concentration of enzyme protein. Hundreds of chemicals have been shown to induce CYP450 and other enzymes. Most of these are lipophiles. These include pharmaceuticals, hormones, organochlorine pesticides, PAHs, including PCBs, and other carcinogenic species [3]. Some pesticides and their decomposition products are powerful inducers. Mirex induces at levels as low as 1 mg/kg. TCDD induces at a level of 1 μ g/kg in some animal species.

Cigarette smoke is a powerful enzyme inducer. It has been shown to induce enzymes in the human placenta, an organ that is essentially inactive toward xenobiotics without induction. Cigarette smoke also lowers plasma levels of some drugs by inducing the enzymes that oxidize those drugs.

When the enzyme that acts on a xenobiotic is induced, the chemical is metabolized faster. It disappears more rapidly and its metabolite forms at an accelerated rate. If the metabolite is not harmful, induction hastens the termination of the effects of the chemical. If, however, the metabolite is toxic, induction intensifies the toxic effect by causing greater quantities of the toxic agent to be formed per unit time.

4.8.9 Inhibition

An inhibiting chemical slows the enzymatic metabolism of toxic chemical. In this instance, if the uptaken chemical itself is the toxin, inhibition will slow the metabolism and intensify its action. If the metabolite of the absorbed xenobiotic is the toxic agent, inhibition will decrease the toxic effect. VC uptake in rats results in a lowering of CYP450 and a corresponding loss of ability to metabolize other xenobiotics [1]. Other inhibitors include diethyl maleate, which inhibits glutathione *S*-transferase, and 1-aminobenzotriazole, which inhibits P450.

4.8.10 Diet and Nutrition

The nutritional state of a person affects the impact and metabolism of absorbed toxic chemicals. Nutrients are chemical compounds that make up the foods that the body uses to function and grow. These include proteins, carbohydrates, fats, vitamins, minerals, and water. The presence of xenobiotics in the body affects that body's nutritional needs. Toxic chemicals can react with nutrients, and those exposed to xenobiotics generally require a diet with increased levels of nutrients in order to receive adequate nutrition.

Phase I and II metabolic reactions require amino acids for enzyme synthesis. A diet that is deficient in amino acid sources (proteins) can result in the individual not synthesizing significant enough enzyme quantities to adequately metabolize xenobiotic species. Protein deficiency results in a decrease in mono-oxygenase reactions (Phase I) and reduces GSH conjugation reactions (Phase II).

Nutrients are chemical compounds that make up the foods that the body uses to function and grow. These include proteins, carbohydrates, fats, vitamins, minerals, and water. Toxic chemicals can react with nutrients. The subject of diet and nutrition is a very complex and voluminous one. A detailed treatment of it is beyond the scope of this book, but it is briefly addressed here. Absorption of chemicals that are diuretics, fever initiators or of chemicals that induce vomiting or diarrhea will increase water requirements. Some xenobiotics interfere with the absorption of carbohydrates from the intestinal tract, and chemicals that bond to lipids and proteins prevent these from being properly metabolized. Still other chemicals interfere with the absorption of vitamins and essential minerals.

4.8.11 Dose and Timing

With a single exposure to a toxic chemical or chemical mixture, the severity of the exposure is determined by the total amount of the exposure (the dose). The higher the dose, the greater the potential for harm. At low levels of exposure, the body is able to metabolize and/or eliminate the chemical(s) at rates rapid enough to prevent serious toxic effects. If the dose is high enough, however, the body's ability to rid itself of the toxin is overwhelmed, threshold levels of toxin(s) are reached, and symptoms of toxic exposure are observed. The threshold levels vary from chemical to chemical and from single chemical to mixture exposures.

When toxic exposures are repeated, the timing as well as the dosage of the exposures is critical. The metabolism and excretion of xenobiotics proceed at finite rates. Stated another way, time is needed for the body to rid itself of the absorbed chemical and its metabolites. Let us consider a situation where the first exposure is at a level that the body can readily metabolize and excrete. If a second toxic exposure to the same chemical at the same level occurs before the body has had sufficient time to cleanse itself, a toxic buildup will occur with the onset of symptoms.

The effects observed from exposure to toxic chemicals can be quite different if a dose is administered all at once or slowly over time. Repeated dosing with low

levels of toxic chemicals can be tolerated even if the total exposure exceeds the threshold value, provided there is sufficient time between doses for the body to rid itself of the toxins.

4.8.12 Genetics

The metabolism of xenobiotics proceeds at different rates for different individuals. This is due to genetic variations. Two examples demonstrate this point. CYP450 enzyme production (required for Phase I metabolism) varies by as much as 30% in healthy individuals. *N*-Acetyltransferase reaction rates (an example of a Phase II metabolism reaction) vary widely. Some individuals acetylate rapidly and others slowly, with the slow acetylators having lower toxic thresholds.

Idiosyncratic differences in humans account for differences in response to toxic exposures. This has led to the pharmacogenomic approach to administering pharmaceuticals to people. This concept is based on the application of drug treatments based on genotype; that is, matching drug and dose to the individual's genetic characteristics. The pharmacogenomic approach has had only limited success because it does not take environmental influences on absorption, distribution, metabolism, and excretion into account. A recent approach, pharmaco-metabonomic phenotyping (PMP), offers the potential to prescribe precise drug treatments. PMP is based on obtaining a pre-dose analysis of the metabolites found in the urine and using this information to predict drug type and dose best suited for the individual. PMP has been demonstrated to successfully predict the liver damaging effects of acetaminophen on laboratory animals [4]. If proven successful in humans, PMP offers not only drug prescription applications, but also a way to predict the extent of toxic effects of single chemicals and mixtures on individuals.

4.9 Oxidative Stress

OS has been advanced to explain many of the hazardous effects of xenobiotic exposure, including carcinogenesis. OS theory as it applies to particular xenobiotic impacts will be addressed in succeeding chapters that address the different target organs of foreign chemicals. The discussion here will be an introductory one. The reader is referred to two papers in the literature and the references contained therein for a more comprehensive discussion [5, 6].

Metabolic processes in the body include reactions that have electron transfer (ET) associated with them. Most xenobiotics or their Phase I enzyme metabolites contain ET moieties. The principal groups include phenols, quinones, aromatic nitro compounds, amines, imines, and metal complexes or complexors.

OS stress theory is based on the tenet that in vivo redox cycling with oxygen results in the formation of reactive oxygen species (ROS). OS is defined as the state in which the body has excessive ROS.

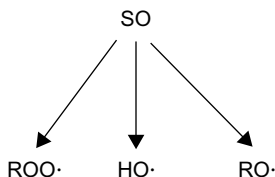


Figure 4.3 In vivo conversion of SO to radical species.



Figure 4.4 Conversion of SO to hydrogen peroxide.

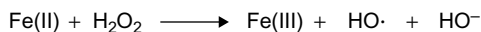


Figure 4.5 The Fenton reaction. Conversion of hydrogen peroxide to hydroxyl radical.

The radical nature of the oxygen molecule facilitates its reaction with various substrates to form radical species. Molecular oxygen can undergo a single electron reduction to form the superoxide (SO). SO can be converted in vivo to peroxides and various oxy radical species, including hydroxyl (OH), alkoxy (RO), and peroxy (ROO) radicals (Figure 4.3). SO is usually disposed of in the body by enzymatic conversion to non-radical hydrogen peroxide (Figure 4.4).

Hydrogen peroxide, which has many metabolic functions in the body, can undergo the Fenton reaction to produce the hydroxyl radical, one of the most powerful ROS (Figure 4.5).

CYP450 enzymes use molecular oxygen to create ROS that mono-oxygenate many natural and xenobiotic species. With natural species and some foreign chemicals, the oxygenation is helpful, producing metabolites that are eliminated from the body. With others, however, such as aromatic hydrocarbons, the ROS metabolites are far more toxic than the parent compounds and create OS. Aerobic life is dependent upon the formation and deactivation of ROS. OS arises when ROS are formed at a rate that exceeds the rate of deactivation.

ROS formation is induced by absorption of many xenobiotics, including haloalkanes, peroxides, benzenoid hydrocarbons, PAHs, phenols, aromatic nitro compounds, aromatic amines, alkylating agents (including epoxides and nitrogen mustards), alkenes (including VC, acrylonitrile, styrene, and 1,3-butadiene), hydrazines, *N*-nitroso compounds, a variety of pesticides, abused drugs, and heavy metals (including Cr, Ni, Pb, and Cd).

4.9.1 Electromagnetic Radiation

Exposure to electromagnetic radiation also causes the production of ROS. Nonionizing ultraviolet (UV) radiation can homolytically cleave hydrogen peroxide to hydroxyl radicals and generate free radical oxygen. High-energy ionizing

radiation (X-rays and gamma rays) breaks molecular bonds, producing free radicals and ions. Ionizing radiation causes the O–H bonds in water to break with the production of the aforementioned hydroxyl radical.

4.9.2 Mixture Effects

Exposures to xenobiotics affect OS adversely by increasing the body's ROS and thereby upsetting the balance between the natural production and elimination of free radicals. OS has been implicated in numerous deleterious conditions brought about by xenobiotic exposures in humans. These conditions include infertility, central and peripheral nervous system effects, respiratory effects, liver and kidney function, cardiovascular effects, and cancer. Each of these will be addressed in the ensuing chapters.

Any absorbed chemical that produces ROS either by itself or via its metabolites affects OS and can adversely affect many organs in the body. Absorption of ROS-producing mixtures will result in greater toxic effects than the absorption of single chemicals. The effects of mixtures can be enhancement of those of the single chemicals or they may result in attacks on organs not targeted by the individual species. The effects of mixtures on OS are to be expected if the individual chemicals and/or their metabolites contain free radicals. This is particularly the case when considering carcinogenesis. Chapter 32 will explore this subject further.

4.10 Receptor–Xenobiotic Interactions

Receptors are macromolecular binding sites for low-molecular-weight molecules (ligands) such as hormones and neurotransmitters. As such they are crucial to the well-being of the body. Xenobiotic ligands bind with receptors and in doing so interrupt the normal functioning of the body.

Receptor interruption can occur in four ways:

1. The xenobiotic may bind with a receptor and thereby block the site from receiving the normal ligand.
2. The binding of the toxic ligand may mimic the normal ligand and initiate a deleterious effect.
3. The xenobiotic may bind to a site adjacent to that where the endogenous molecule binds, causing the complex to be sterically distorted and resulting in changes that affect the normal functioning of the receptor.
4. Macromolecules in the body that normally do not act as receptors may bind xenobiotics and thereby induce physiological changes.

Receptor–xenobiotic interactions have been associated with immune, CNS, endocrine, cardiovascular system (CVS), developmental, and reproductive system effects as well as with carcinogenesis. A sampling of toxic chemicals that bind with receptors and their effects are listed in Table 4.3.

The subject of receptor–xenobiotic interaction will be addressed further in subsequent chapters.

Table 4.3 Receptor-Binding Xenobiotics and Their Effects

Chemical	Effect	Reference
Dioxin	Carcinogenesis	[7]
Di- <i>n</i> -butyl phthalate	Reproductive developmental	[8]
Polychlorinated biphenyls	Carcinogenesis	[9]
Chlorpyrifos	CNS, CVS	[10]
Parathion	CNS, CVS	[10]
Polynuclear aromatic hydrocarbons	Reproductive	[11]
<i>p</i> -Nonyl phenol	Endocrine	[12]

4.11 Endocrine Disruptors

The endocrine system is comprised of a network of hormone-producing glands. These glands include the pituitary, thyroid, adrenal, thymus, pancreas, ovaries, and testes. The hormones produced are released in carefully measured doses. They serve as chemical messengers that regulate many of the body's functions, including growth, development, maturation, reproduction, and the operation of various organs. Small quantities of hormones are essential for normal body function. Too much of a given hormone as well as too little of it can be deleterious to health, development, and reproductive capability.

The World Health Organization (WHO) defines endocrine-disrupting compounds (EDCs) as, "exogenous substances that alter function(s) or the endocrine system and consequently cause adverse health effects in an intact organism, or its progeny or (sub)-populations" [13]. Endocrine disruptors can act in any of the four different ways [14]. These are:

1. Mimicking the effects of endogenous hormones, by attaching themselves to hormone receptor sites and thus increasing hormone levels in the body.
2. Antagonizing the effects of endogenous hormones, thus depriving the body of needed hormones.
3. Disrupting the synthesis and metabolism of endogenous hormones, either by excessively promoting these reactions or retarding them.
4. Disrupting the synthesis and metabolism of endogenous hormone receptors and interrupting the body's uptake of hormones at vital areas.

4.11.1 Effects on Humans

The effects of endocrine-disrupting chemicals were first discovered in wildlife in the 1970s. It was found that extremely low concentration levels of these can have powerful deleterious effects on the reproduction of wildlife. Human effects were not studied until much later because most EDCs are neither mutagenic nor acutely toxic at the ambient concentrations found to have endocrine disruption effects on wildlife. It was also believed that effects on birds and turtles were not necessarily indicators of human toxicity. This, however, turned out to be exactly the case. Though toxic

Table 4.4 Endocrine-Disrupting Chemicals (EDCs) [16, 17]

Pesticides and herbicides	Pyrethroids (synthetic)
2,4-D	Simazine
2,4,5-T	Tributyl tin
Alachlor	Toxaphene
Aldicarb	Industrial chemicals
Amitrole	Bisphenol A
Atrazine	Dioxin
Beta-HCH	<i>p</i> -Nonyl phenol
Carbaryl	Polybrominated biphenyls (PBBs)
Chlordane	Polychlorinated biphenyls
DDT and metabolites	Pentachlorophenol (PCP)
Dicofol	Phthalates
Dieldrin	Styrenes
Endosulfan	Triclosan
Heptachlor and H-epoxide	Heavy metals
Lindane	Cadmium
Methoxychlor	Lead
Mirex	Mercury
Oxychlordane	
Parathion	

effects of chemicals are not always similar for different species of animals, they are just that for endocrine disruptors. The effects of EDCs on birds and amphibians are exactly analogous to those on humans.

Though EDCs can effect immunological responses, the most studied effects of EDCs are the reproductive and developmental ones. These, which include male and female reproductive disorders, trans-generational and developmental effects on the fetus in utero, and the developing child will be addressed further in the infertility and development chapters. The reader is referred to the epic work of Theo Colborn, Dianne Dumanoski, and John Peterson Myers, *Our Stolen Future* [15], to the aforementioned WHO report [13] and to the literature [16, 17] for review discussions of the subject.

4.11.2 Endocrine-Disrupting Chemicals

Chemicals known to be human endocrine disruptors include dioxin, PCBs, DDT and other pesticides, diethylstilbestrol, some phthalate ester plasticizers, and heavy metals. Table 4.4 lists some endocrine-disrupting chemicals.

Hormones of both synthetic and biological origin are known endocrine disruptors. The best known of these is diethylstilbesterol (DES), a synthetic estrogen that was prescribed by physicians to prevent spontaneous abortions in women from 1948 to 1971. Daughters of women who took DES have suffered a host of reproductive problems, including a reduction in fertility, abnormal pregnancies, immune system disorders,

Table 4.5 Synthetic and Biological Origin Hormones
That Are Endocrine Disruptors

Synthetic hormones	Biological hormones
Diethylstilbesterol	17- β -Estradiol
17- α -Ethinylestradiol	Estriol
17- β -Erenbolone	Estrone
	Progesterone
	Testosterone

periods of depression, and early onset of vaginal clear-cell adenocarcinoma reproductive tract cancer. Known hormonal endocrine disruptors are listed in Table 4.5.

4.11.3 EDC Mixtures

The discussion of EDCs to this point has addressed responses to single chemicals. Mixtures of hormone disruptors have not been well-studied, but the example of the mixture effects of DDT and dichlorodiphenyldichloroethylene (DDE) is an illustration of how an EDC mixture can produce unexpected effects.

The pesticide DDT is an estrogen mimic that affects the body by elevating hormone levels. This, however, is not its only effect. DDE, the metabolite of DDT, is a fat-soluble species that persists for long periods of time in the human body that has the opposite effect of DDT. DDE depletes hormones by accelerating their breakdown and elimination. This leaves the body with a short supply of not just estrogen, but testosterone and other steroid hormones as well [18].

More recent research has identified low-dose mixtures of estrogenic, thyroid disrupting, and anti-androgenic chemicals as endocrine disruptors [19, 20].

4.12 Immunotoxicology

Immunotoxicology is the study of the adverse health effects of xenobiotics on the immune system. A thorough review of the immune system and immunotoxicology is beyond the scope of this book. A brief outline is given here. The reader is referred to the literature referenced for good introductions to this topic [21–23].

Lymphatic tissues constitute the principal parts of the immune system. The central immune system lymphatic tissues are bone marrow and the thymus gland. The peripheral lymphatic tissues are spleen, lymph nodes (that are distributed throughout the body), tonsils, and adenoids. There are also lymph tissue agglomerates that are present in the gastrointestinal tract, respiratory system, and skin, making lungs, gut, and skin particularly vulnerable to attack by chemical toxins.

Immunotoxicological impacts include molecular and structural effects in immune tissues and organs, cellular pathology, reductions in immune cell numbers, retarded maturation of immune system cells, and altered immune system antibody production. These adverse effects are manifested by two types of reaction—immunosuppression and immunostimulation.

Table 4.6 Partial List of Immunosuppressive Chemicals

Benzene	Tin
Toluene	Methylmercury (MeHg)
Xylenes	Nitrogen dioxide
Styrene	Sulfur dioxide
Benzo[a]pyrene	Ozone
Phosgene	Aldrin
Ethanol	Dieldrin
Carbon tetrachloride	Endrin
<i>trans</i> -1,2-Dichloroethylene	Chlordane
1,2-Dichloroethane	Heptachlor
Methylene chloride	Lindane
Carbon tetrachloride	Dichlorodiphenyl trichloroethane
Trichloroethane	Malathion
Tetrachloroethane	Parathion
2-Methoxyethanol (2-ME)	2,4-D
Ethyl acrylate	2,4,5-T
Benzidines	Asbestos
2,3,7,8-Tetrachlorodibenzo- <i>p</i> -dioxin	Silica
Polychlorinated biphenyls	Epoxy resins
Arsenic	UV radiation
Lead	Ionizing radiation
Cadmium	

4.12.1 Immunosuppression

In immunosuppression, one or more parts of the immune system are impacted. This results in impaired immune system function and reduced resistance to foreign chemical and biological agents that attack the body and can lead to increased incidence of infectious disease and cancer.

More than 400 chemicals have been identified as immunotoxins [21, 24]. These include single-ring aromatic hydrocarbons, aromatic amines, PAHs, pesticides, hydroxyethers, oxidant gases, heavy metals, halogenated aliphatic hydrocarbons, halogenated aromatic hydrocarbons (including PCBs), dioxins, and lung fibers. Though they are not strictly chemicals, exposure to some wavelengths of electromagnetic radiation also results in immunotoxic effects. A partial list of immunosuppressive chemicals is presented in Table 4.6.

Stress and exposure to electromagnetic radiation (UV or ionizing radiation), though not chemicals, are immunosuppressants. People who bask under artificial UV sun lamps have been found to have suppressed immune responses, as have bereaved individuals. It is known, for example, that the combined effect of exposure to ionizing radiation and physical trauma (burns or wounds) produces a synergistic immunosuppressant effect.

Mixtures of chemicals have been shown to seriously impact the immune system. The following examples are illustrative:

Table 4.7 Partial List of Immunostimulants

Beryllium
Platinum
Thioglycolates (ammonium, sodium, potassium)
Formaldehyde
1,2-Propanediol,2-methylmonomethacrylate
Methyl methacrylate
Tetramethylene diacrylate
Toluene-2,4-diisocyanate
Methylenebisthiocyanate
Trimellitic anhydride
Sodium sulfite
Chlorine

1. Toluene alone is not a severe immunotoxin. When administered in combination with benzene, a potent immunotoxin, toluene enhances the immunotoxic effects of benzene. It does so by competing with benzene for Phase I metabolizing enzymes, thereby allowing benzene concentrations in the body to remain higher than if benzene were present alone [25].
2. The combination of cigarette smoking and exposure to aromatic hydrocarbons (benzene and its homologs) had a synergistic effect, resulting in a greater reduction of circulating antibody levels than expected from an additive effect [26].
3. Petroleum refinery workers, who are regularly exposed to mixtures of hydrocarbons, have been found to have depressed immune system output [27].

During periods of immune system response, e.g., at times of infectious disease, CYP450-dependent metabolism of xenobiotics is reduced. This effect is attributed to the production of interferon by the immune system as it responds to a challenge. Human interferon has been shown to suppress the metabolism of BaP in laboratory animals [21].

4.12.2 Immunostimulation

Immunostimulation can lead to allergic disease. Allergy to chemical and biological agents can take several forms. These include allergic contact dermatitis (ACD); sensitization of the respiratory tract, including asthma and/or rhinitis; systemic allergic reactions, including anaphylaxis; and gastrointestinal effects. Immunostimulation can also lead to autoimmunity, wherein immune cells attack the body.

An antigen is a molecule that causes an immune response in a person predisposed to react by genetics and/or environmental exposure. Upon one's first exposure, such a person's body will generate immunoglobulin E (IgE) antibodies. These IgE antibodies, found in the nose, tongue, lungs, skin, and intestinal tract, react specifically with the invoking antigen upon subsequent exposure, setting off an allergic response.

Chemical antigens known to stimulate immune responses in humans include formaldehyde, isocyanates, acrylates, metals, sulfites, and anhydrides. Table 4.7 lists a number of these compounds.

Table 4.8 Mixtures That Evoke Immunostimulant Effects

Paints	Air pollution (smog)
Detergents	Chemical flavors
Cigarette smoke	Artificial sweeteners
Automobile and diesel exhaust	Organic solvents
Cosmetics	

Table 4.9 Body Responses to Toxic Chemical Exposures

Phase I metabolism	Receptor interaction
Phase II metabolism	Endocrine disruption
Enzyme induction	Immunosuppression
Enzyme inhibition	Immunostimulation
OS enhancement	

Many chemical mixtures, in which specific antigens have not been identified, also evoke immunostimulant responses. These are listed in Table 4.8 [28]. Many of these will be considered in some detail in subsequent chapters.

4.13 Multiple Site Responses

As discussed earlier, when the human body is exposed to toxic chemicals, multiple responses are induced. These responses are summarized in Table 4.9.

It goes without saying that not all xenobiotics illicit all the responses listed in Table 4.9. Many toxins, however, do illicit multiple responses. Complicating the picture is the fact that not all bodily responses are primary ones; that is, direct reactions to the absorbed toxin. Secondary reactions can and do occur. Examples of these are a metabolite (and not parent compounds) that is actual toxins, OS inhibiting the action of a free radical inhibitor, and immunosuppression impacting metabolism.

Table 4.10 lists a number of xenobiotics that have multiple impacts on the body. It is hypothesized here that chemicals with greater numbers of impacts are more dangerous to the body's health than those with single effects. As can be seen from Table 4.10, all the chemicals listed have multiple impacts. All of these chemicals are pervasive throughout the environment. Based on the multiple responses they illicit and their association with numerous health effects, they may be considered among the most dangerous environmental toxicants. There are, of course, many chemicals whose single bodily impact is immediately life threatening (e.g., cyanides) and no attempt is being made here to assign relative total toxicity values based on numbers of bodily responses. Such an assignment is particularly difficult due to numerous interactions between the body's systems.

Even though a chemical is known to hit multiple organs, it does not always impact them all.

Table 4.10 Xenobiotics with Multiple Impacts on the Body

Chemical	Body Responses Illicited				
	MET	RB	END	OS	IM
PCBs	X	X	X	X	X
TCDD	—	X	X	—	X
Di- <i>n</i> -butyl phthalate	X	X	X	X	—
Chlorpyrifos	X	X	X	X	—
Parathion	X	X	X	X	X
PAHs	X	X	X	X	X
<i>p</i> -Nonyl phenol	X	X	X	X	—
Benzene	X	X	X	X	X
Styrene	X	X	X	X	X
Mercury	—	X	X	X	X
Lead	—	X	X	X	X

MET, metabolized by the body; RB, receptor binding; END, endocrine disrupting; OS, oxidative stress producing; IM, immune system suppressants. “X” denotes illicited responses and “—” denotes no known response.

4.14 Mixture Effects

Virtually every breath we take, every drop of water that passes our lips or bathes our skin, and every morsel of food we eat contains mixtures of xenobiotic chemicals in it.

As discussed earlier, the absorption of single toxic chemicals can illicit several body responses. When mixtures are absorbed, the body reactions may be considered to be the sum of those associated with all components of the mixtures. This, however, is an oversimplified approach. The effects of mixtures are not always the sum of all their parts for one of the following reasons:

1. Interactions among the mixture components produce new chemical species. For example, the concurrent inhalation of ammonia or amines and chlorine produces the extremely toxic chloramines.
2. Transport of hydrophiles to parts of the body they would not ordinarily reach by their solution in lipophiles. Transport of xenobiotics to unexpected parts of the body can result in body responses not found for single chemical absorption. The inhalation of formaldehyde and xylene, for example, results in formaldehyde reaching the lower airways. This does not happen when formaldehyde alone is inhaled [29].
3. The interaction of a toxic chemical with its metabolite or the metabolite of another species. Phase I metabolism of xenobiotics produces hydrophiles. These hydrophiles may dissolve in lipophiles and be transported in the body. As an example, benzene is metabolized to the leukemogen, hydroquinone. Hydroquinone dissolves into residual benzene and is transported into the bloodstream [30].
4. Potential saturation, or overwhelming, of the body’s reaction potential. The body adapts to toxic exposure by increasing its detoxifying enzyme production and immune response.

This allows the individual to “get used to” ever-increasing exposure to a toxicant (an example is the adaptation to ever-increasing quantities of products containing ethanol). Ultimately, the body’s breaking point is reached and the individual experiences end-organ failure. In the example of ethanol, cirrhosis of the liver may occur [31].

5. Interaction with chemicals previously absorbed. An example of this is the toxic effect of acetaminophen when taken some time after ingestion of ethanol [2].
6. Different chemicals can produce the same metabolites, thereby enhancing the effects of simultaneous exposure. An example is the combination of *n*-hexane and methyl-*n*-butyl ketone. Both are metabolized to 2,5-hexanedione [31].
7. Competition of mixture components for the same metabolic sites can expand the residence time of one or more of the toxins. An example of this is the simultaneous uptake of benzene and toluene, which leads to a slowdown of the metabolism of benzene [32].

The examples of the effects just described are, unfortunately, few in number. This makes predicting the toxic effects of mixtures very difficult and underscores the importance of the empirical approach. As discussed in Chapter 2, it has been found empirically that human exposure to combinations of lipophiles and hydrophiles produces unanticipated effects. The underlying mechanism(s) for this phenomenon remain unknown.

As discussed in Section 4.9, electron transport (ET) and generation of ROS has been associated with numerous diseases and cancers [5]. Many xenobiotics undergo Phase I metabolism and in the process produce ROS. The absorption and metabolism of mixtures of chemicals accordingly increase the quantities of ROS and thereby the OS. No association, however, has been made to date between toxic effects attributed to OS and exposures to mixtures.

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Part II

Exposures to Chemical Mixtures

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5 Scope and Sources of Toxic Exposures

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5.1 Scope of Exposure: Introduction

Since Friedrich Wohler first synthesized urea in 1828, it is estimated that more than 1 million chemicals that were previously unknown in our environment have been synthesized. There are more than 80,000 chemicals manufactured and imported into the United States each year. People are exposed to most of these by air pollution, water pollution, foods and food chain transfers, soil contamination, household use of chemical products, the use of personal care and pharmaceutical products, and industrial contact. Exposure begins before birth in utero and continues throughout life. The different modes of exposure will be dealt with separately in the following chapters.

5.2 Toxic Release

The U.S. Environmental Protection Agency (EPA) is charged with collecting and reporting information about chemical releases and waste management in the United States, the Toxics Release Inventory (TRI). Under the Emergency Planning and Community Right-To-Know Act of 1986 (EPCRA), industrial facilities are required to report their environmental releases and waste management practices to EPA each year. For the year 2002, EPA collected data from nearly 20,000 industrial facilities about the releases of approximately 650 toxicants to the air, water, and ground, and the amounts of chemicals that were recycled, treated, burned, or otherwise disposed of on site. For 2002, greater than 4 billion pounds of toxic chemicals, including more than 70 million pounds of known carcinogens, were reported under TRI. The complete list of TRI chemicals is available on the EPA website [1].

TRI is the most detailed source of information about toxic chemical releases. TRI, however, seriously underreports the total toxic chemical releases for the following reasons:

1. TRI does not cover all industries. Prior to 1998, for example, metal mining and electric utilities were not required to report their toxic chemical releases.
2. TRI reports on less than 1% of the 80,000 chemicals annually manufactured and imported into the United States. It covers only about 650 of the chemicals in use in the United States.
3. Reporting companies estimate their emissions by using emission factors rather than by actually monitoring their emissions.
4. TRI does not require the reporting of the quantities of toxic chemicals actually used and the amounts of these chemicals that remain in products they manufacture and distribute.
5. TRI does not report on the toxic exposures that result when people are exposed to the chemical products that are put into the stream of commerce.

5.3 Unknown Toxicities

Of the approximately 80,000 chemicals that are in commercial use in the United States, even basic toxicity information is missing for nearly 75% of the top 3000 high-production volume species [2]. Essentially nothing is known about the toxicities of mixtures of these chemicals.

The vast majority of the 80,000 chemicals in use have been synthesized since World War II. It is estimated that 3000–5000 new chemicals are introduced each year. Virtually every chemical that is manufactured is ultimately released into the environment. Barely 60 years have transpired since the large-scale release of new chemicals into the environment started. This is a short time span in the evolutionary time frame, meaning that the human species has not had time to adapt to the new chemicals in the environment [3]. Further complicating any chance to accurately assess the impact is the fact that new chemicals are constantly being introduced and, accordingly, new chemical mixtures are constantly being created.

Not only new chemicals, but also new, heretofore unknown, classes of chemicals are constantly being introduced. Following are examples of such chemicals:

1. Organochlorine and organophosphate pesticides were synthesized and released into the environment with the sole purpose of killing living organisms considered to be pests. No consideration was given to their impacts on humans and other non-pests until widespread problems appeared [4].
2. PCBs were introduced for their fire-retardant properties without toxicological evaluation. The health effects that ensued are still being felt today, more than 20 years after they were banned [5].
3. Plasticizers (e.g., phthalate esters and *p*-nonylphenol) were introduced to impart flexibility to polyvinyl chloride (PVC) and other plastics. Their developmental effects on children were subsequently discovered [6].
4. Recently, an exciting discovery was announced. Researchers have synthesized catalysts that mimic enzyme oxidation [7]. This could turn out to be a truly exciting development.

It begs the question, “what will the effects of this new class of compounds be when they are released into the environment?” The answer is unknown. The paper announcing this advance made no mention of any toxicity testing of these catalysts. It is not the intention here to disparage this new research. Rather, it is being used as an illustration of how newly synthesized compounds are viewed only for their uses, with little or no attention being paid to their toxicities. Such approaches have resulted in the release of DDT, PCBs, and other toxic chemicals whose use was well intentioned.

5. In the past few years, nanotechnology has surged into the forefront of research and technology development. Many new and novel applications are being found on an almost daily basis for these ultrafine particles, including medical ones. It has been recently reported, for example, that nanoparticles have been used as carriers to deliver very low doses of Fumagillin, a drug that can inhibit the growth of new blood vessels that feed atherosclerotic plaques directly to the base of the plaques [8]. Carbon nanotubes (CNTs) are extensively employed in this new science. CNTs have unique electrical, mechanical, and thermal properties that give them wide-ranging applicability in electronics, aerospace, computer, and other areas. CNTs have very small particle size (less than 2.5μ) and pose serious health hazards when inhaled. They have been found to elicit pathological changes in the lungs, impair normal respiratory function, retard bacterial clearance, damage the mitochondrial DNA in the aorta, increase the level of aortic plaque, and induce atherosclerotic lesions in the brachiocephalic artery of the heart [9]. Fine carbon particles such as those in CNTs readily absorb a multitude of organic molecules. Such absorption results in the transport of these xenobiotics into the body. In another recent study in animals, it has been found that nanosized particles of manganese oxide (less than 100 nm in diameter), at concentrations typically as inhaled by factory welders, follow a rapid movement from the nasal cavity to the brain [10]. The effects of a buildup of these particles on the brain are believed to be associated with inflammation and cellular stress response. Nanotechnology is well intentioned. The benefits to science and humankind have been enormous and new uses for CNTs are being found almost every day. The need to control their emissions into the environment, however, cannot be overstated. Nanoparticle toxicology will be explored further in Chapter 34.

5.4 Proliferation

Toxic chemicals are now found in virtually every corner of the globe. The highest mountains, depths of the ocean, and far reaches of the polar regions are contaminated with toxic chemicals. This subject has been well explored and well written about by numerous researchers and writers. Carson's *Silent Spring* [11] and Colborn, Dumanoski, and Myers *Our Stolen Future* [6] are two well-known sources. Toxicants are spread by wind, carried by water, and bioaccumulated by the various food chains to ultimately reach humans. It is beyond the scope of this book to examine the spread of toxic chemicals in the environment. One example, however, is illustrative of the extent of this phenomenon.

Polybrominated diphenyl ethers (PBDEs) are synthetic chemicals that are used as flame retardants in clothing, building materials, airplane and car seats, electronic components, and other consumer products. PBDEs are introduced into the environment from discharges and leaks at manufacturing facilities, leaks from manufactured

products, and from land fills containing PBDE products. Like PCBs, PBDEs have low vapor pressures, are lipid soluble, and are resistant to enzymatic metabolism. They do, however, become airborne when silt and dust particles to which they are adhered dry out and get wind-blown great distances to where they are deposited on land and sea. Though essentially water insoluble, they adhere to lipophilic solids and are carried in ocean currents. They are ultimately passed up the food chain by bioaccumulation. PBDEs, like PCBs and chlorinated pesticides before them, have reached the Arctic. They have been found in Arctic cod, ringed seals, polar bears, and beluga whales [12].

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6 In Utero Exposure

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6.1 Fetal Sensitivity

Exposure to toxic chemicals begins in utero, with the fetus exposed to all the chemicals that the mother has in her body. The developing fetus is particularly sensitive to toxic chemical attack. Though all systems and organs are under development during gestation, not all grow or mature at the same rate or in the same time frame. This phenomenon results in the association of developmental problems from exposures during one time in pregnancy and lack of such problems from identical exposures during other gestation periods. The association between developmental problems and toxic chemical exposures will be examined in more detail in a subsequent chapter of this book. The following effects, however, are worthy of note here:

1. A developing fetus is much smaller than an adult or even young child. The effects of chemical exposure are, therefore, much greater for the fetus. An exposure of 10ppb of PCBs will have a negligible effect on an adult, but will impair the brain development of a fetus.
2. The fetus has an immature, porous blood–brain barrier, allowing greater exposures to the developing brain.
3. The fetus has lower levels of some chemical-bonding proteins, allowing a greater accessibility to target organs.
4. The developing fetus's organs are rapidly developing and are more vulnerable to toxic attack than fully developed organs.
5. In the fetus, the systems and organs that detoxify and excrete toxic chemicals are not fully developed. This leads to longer residence times and correspondingly greater toxic effects.
6. Many of the effects of toxic exposure in utero are not manifested until after birth. Such effects include the onset of autism and reproductive problems.

6.2 Toxic Chemicals in the Blood of Newborns

In a study commissioned by the Environmental Working Group (EWG), the blood of 10 American newborn babies born in U.S. hospitals in August and September of

Table 6.1 Classes of Compounds and Their Sources Found in EWG Newborn Babies Study

Class of Compound	Source
Mercury	Pollutant from coal-fired power plants
PAHs	Combustion of fossil fuels, tobacco smoke
Polybrominated dibenzo-dioxins and -furans	Contaminants of brominated flame retardants
Perfluorinated chemicals	Breakdown products from Teflon and fabric protectors
Organochlorine pesticides	Crop application, environmental residues, bioaccumulation
Polychlorinated dibenzo-dioxins and -furans	By-products of PVC production, incineration
PBDE	Flame retardant in foams, electronics
Polychlorinated naphthalenes	Wood preservatives, lubricating oils
PCBs	Transformers and other electrical equipments

2004 was analyzed for 413 industrial and consumer product chemicals [1]. The analysis discovered a wide variety of pollutants, including mercury, pesticides, polynuclear aromatic hydrocarbons (PAHs), and PCBs. In all, 287 different chemicals were found in the newborn babies' blood, with the average baby having 200 of these at birth. A list of the classes of compounds found and their sources is given in Table 6.1.

6.3 Toxic Hazards of Fetal Toxicants

Of the 287 different chemicals found in the EWG study, four are particularly noteworthy for the effects they bring about in later life. These chemicals are dioxin, methylmercury, PCBs, and DDE, the metabolite of the pesticide DDT.

Dioxin exposures during fetal development have been associated with endocrine-related cancers (breast and uterine) in women. Dioxin exposure in utero has also been tied to male reproductive effects. Men who are exposed to dioxin in utero father more than twice as many girls as boys. It is also associated with infant death and birth defects.

PCB exposure in the womb is associated with lower IQ scores in children and with abnormal menstrual cycles in women.

Methylmercury exposure in utero is associated with reduced brain function and a doubling of the risk of heart attacks and other cardiovascular problems.

DDE, the long-lived metabolite of DDT, is associated with premature birth and low birth weight. Low birth weight is considered an indicator of hypertension, cardiovascular disease, and the onset of type-II diabetes later in life.

The above describes what is known about only a few of the 287 chemicals detected in the blood of newborns in the EWG study. Table 6.2 lists the health effects or body systems known to be affected by the chemicals found. Many of the chemicals are associated with multiple health effects. It should be noted that EWG points

Table 6.2 Health Effect or Body System Impacted by the 287 Chemicals Found

Cancer	Cardiovascular system
Birth defects	Central nervous system
Developmental retardation	Peripheral nervous system
Male reproductive system	Vision
Female reproductive system	Hearing
Endocrine system	Skin
Immune system	Liver
Respiratory system	Kidney
Gastrointestinal system	

out that the 287 compounds were those that were particularly tested for and that no doubt many others would have been found as well had the analysis been directed at those.

6.4 Mixtures

The full health effect impact of the 287 toxicants found on the 10 babies tested is impossible to ascertain. The chemicals found include many lipophiles and hydrophiles and the combinations possible are almost endless. Further complicating the health picture is the continued exposure of these babies to the same and other xenobiotics as they develop. Such exposure gives rise to still more toxic mixtures.

There are no known direct studies on the toxic effects of chemical exposures on the developing fetus. It is known, however, that children of tobacco smokers (tobacco smoke is a mixture of multiple lipophiles and hydrophiles) have unusually high incidences of ADHD, autism, and other developmental disorders. These and other mixture effects will be examined more closely in subsequent chapters. This chapter has aimed to alert the reader to the fact that toxic exposure begins at conception and impacts the fetus throughout gestation and beyond.

Reference

- [1] Environmental Working Group, Body burden study. www.ewg.org/reports/bodyburden, 2004.

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7 Air Pollution

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7.1 Introduction

Air pollution is a primary source of exposure to a wide variety of toxic chemicals. The air we breathe contains numerous xenobiotics as well as increased concentrations of naturally occurring chemicals such as ozone and particulate matter. The dangers posed by these substances are not limited solely to inhalation. Skin contact, too, is a primary source of exposure and many lipophilic chemicals are readily absorbed from the vapor phase through the skin. These lipophiles have the propensity to carry hydrophiles with them.

The sources of air pollutants include industrial as well as consumer use of chemicals. Virtually every human activity in the twenty-first century results in the release of volatile and/or particulate matter xenobiotics into the air. Such activities include unexpected ones such as opening a loaf of bread (propionic acid is released from almost all packaged bread [1]) and changing a baby's diaper (disposable diapers contain several VOCs introduced during their manufacture [2]).

Most chemicals used by people become airborne either by volatilization or from being blown as aerosols or particulates by air-moving devices and wind. The hazards of particulate matter are, to a great extent, determined by their size. Particles larger than 10 μ in diameter are filtered out in the upper respiratory tract and expelled. All

particles with a diameter of 10μ or smaller (PM₁₀) reach the lungs and are harmful. Particles with diameters of less than 2.5μ (PM_{2.5}) are particularly dangerous because they reach deep into the lung tissue. This subject was discussed in Section 5.3 and will be examined in more detail in Chapter 17.

Air pollutants can be considered in three contexts: pervasive, confined, and breathing zone.

1. *Pervasive air pollutants*: Those air pollutants that are present in the general outdoor atmosphere to which all individuals will be exposed. These result from releases of toxicants into the air and from chemical reactions that take place in the atmosphere.
2. *Confined air pollutants*: Those air pollutants that are present in a building, a room, a confined area, or an outdoor area with limited circulation to which all individuals present will be exposed. These result from limited releases of toxicants into well-defined areas.
3. *Breathing zone air pollutants*: Those air pollutants that are present in appreciable concentration only in a very small area, confined to the breathing zones of those immediately present. Breathing zone air pollutants do not pose threats to others close by, even if they are in the same room or area.

7.2 Pervasive Air Pollutants

Pervasive air pollutants can be vapors, aerosols, or particulates. They primarily arise from industrial manufacturing, mining, agricultural activity, fires, and fossil-fuel combustion.

The U.S. Environmental Protection Agency (EPA) is charged with addressing air pollution under the Clean Air Act. The poor air quality found in California has led the State of California to establish the California Air Resources Board (ARB), which also addresses this subject. EPA has established a list of hazardous air pollutants [3] and ARB has established a Toxic Air Contaminant (TAC) Identification List [4]. Numerous other literature references identify still other known air pollutants. Table 7.1, toxic chemicals in the air, which was compiled from these sources, shows the range of pervasive toxic chemicals that are found in the air we breathe.

The chemicals listed in Table 7.1 are those that are commonly found in the atmospheric air of the United States. Not all these species are found in all locations, and the concentrations of these xenobiotics vary with proximity to source points and prevailing meteorological conditions. On the other hand, numerous other air pollutants are found in different locations.

The EPA National Air Toxics Assessment, which is based on the analysis of 33 representative air pollutants, is used to produce results that are representative of air quality and its effects on human health [5]. These are listed in Table 7.2.

7.3 Chemical Reactions in the Air

As can be seen from Table 7.1, huge numbers of chemical species are regularly emitted into the air. With solar radiation acting as a catalyst, many of these chemicals

Table 7.1 Toxic Chemicals in the Air

Acetaldehyde	Ethylidene dichloride
Acetamide	Fine mineral fibers
Acetonitrile	Formaldehyde
Acetophenone	Glycol ethers
2-Acylaminofluorene	Heptachlor
Acrolein	Hexachlorobenzene (HCB)
Acrylamide	Hexachlorobutadiene
Acrylic acid	Hexachlorocyclopentadiene
Acrylonitrile	Hexachloroethane
Allyl chloride	Hexamethylene-1,6-diisocyanate
4-Aminobiphenyl	Hexamethylphosphoramide
Ammonia	Hexane
Aniline	Hydrazine
<i>o</i> -Anisidine	Hydrochloric acid
Antimony compounds	Hydrogen fluoride
Arsenic compounds (including arsine)	Hydrogen sulfide
Asbestos	Hydroquinone
Benzene	Isophorone
Benzidine	Lead compounds
Benzotrichloride	Lindane
Benzyl chloride	Maleic anhydride
Beryllium compounds	Manganese compounds
Biphenyl	Mercury compounds
Bis(2-ethylhexyl)phthalate	Methanol
Bis(chloromethyl)ether	Methoxychlor
Bromoform	Methyl bromide
1,3-Butadiene	Methyl chloride
<i>n</i> -Butanol	MEK
Cadmium compounds	Methyl hydrazine
Calcium cyanamide	Methyl iodide
Caprolactum	Methyl isobutyl ketone
Captan	Methyl isocyanate
Carbaryl	Methyl methacrylate
Carbon disulfide	Methyl <i>t</i> -butyl ether
Carbon monoxide	4,4-Methylene bis(2-chloroaniline)
Carbon tetrachloride	Methylene chloride
Catechol	Methylene diphenyl diisocyanate
Chloramben	4,4-Methylenedianiline
Chlordane	Naphthalene
Chlorine	Nickel compounds
Chloroacetic acid	Nitrates and nitric acid
2-Chloroacetophenone	Nitrogen oxides (NO _x)
Chlorobenzene	4-Nitrobiphenyl
Chlorobenzilate	4-Nitrophenol
1-Chloro-1,1-difluoromethane	2-Nitropropane
Chloroform	<i>N</i> -Methyl-2-pyrrolidone
Chloromethyl methyl ether	<i>N</i> -Nitroso- <i>N</i> -methylurea
Chloroprene	<i>N</i> -Nitrosodimethyleneamine
Chromium compounds	<i>N</i> -Nitrosomorpholine

(Continued)

Table 7.1 (Continued)

Cresols	Ozone
Cresylic acid	Parathion
Cumene	Pentachloronitrobenzene
Cobalt compounds	PCP
Coke oven emissions (including carbon black)	Perchloroethylene
Copper compounds	Phenol
Cyanides (sodium and potassium)	<i>p</i> -Phenylenediamine (PPD)
2,4-D, salts, and esters	Phosgene
DDE	Phosphine
Diazomethane	Phosphorus
Dibenzofurans	Phthalic anhydride
1,2-Dibromo-3-chloropropane	PCBs
Dibutylphthalate	PAHs
<i>p</i> -1,4-Dichlorobenzene	1,3-Propane sultone
3,3-Dichlorobenzidine	Beta-propiolactone
1,1-Chloro-1-fluoroethane	Propionaldehyde
Dichloroethyl ether	Propoxur
1,3-Dichloropropene	Propylene
Dichlorvos	Propylene dichloride
Diesel particulate matter	Propylene oxide
Diethanolamine	1,2-Propyleneimine
<i>N,N</i> -Diethyl aniline	Quinoline
Diethyl sulfate	Quinone
3,3-Dimethoxybenzidine	Radionuclides (including radon)
Dimethyl aminoazobenzene	Selenium compounds
3,3'-Dimethyl benzidine	Sulfuric acid (including sulfur dioxide and trioxide)
Dimethyl carbamoyl chloride	Styrene
Dimethyl formamide (DMF)	Styrene oxide
1,1-Dimethyl hydrazine	TCDD
Dimethyl phthalate	1,1,2,2-Tetrachloroethane
Dimethyl sulfate	Titanium tetrachloride
4,6-Dinitro- <i>o</i> -cresol and salts	Toluene
2,4-Dinitrophenol	2,4-Toluene diamine
2,4-Dinitrotoluene	2,4-Toluene diisocyanate
1,4-Dioxane	<i>o</i> -Toluidine
1,2-Diphenylhydrazine	Toxaphene
Epichlorohydrin	1,2,4-Trichlorobenzene
1,2-Epoxybutane	1,1,1-Trichloroethane
Ethyl acetate	1,1,2-Trichloroethane
Ethyl acrylate	TCE
Ethyl benzene	Trichlorophenols
Ethyl carbamate	Triethylamine
Ethyl chloride	Trifluralin
Ethylene dibromide	2,2,4-Trimethylpentane
Ethylene dichloride	Vinyl acetate
Ethylene glycol	Vinyl bromide
Ethylene imine	VC
Ethylene oxide	Xylenes
Ethylene thiourea	

Table 7.2 Thirty-Three Representative Air Pollutants

1. Acetaldehyde	18. Formaldehyde
2. Acrolein	19. HCB
3. Acrylonitrile	20. Hydrazine
4. Arsenic compounds	21. Lead compounds
5. Benzene	22. Manganese compounds
6. Beryllium compounds	23. Mercury compounds
7. 1,3-Butadiene	24. Methylene chloride
8. Cadmium compounds	25. Nickel compounds
9. Carbon tetrachloride	26. Perchloroethylene
10. Chloroform	27. PCBs
11. Chromium compounds	28. PAHs
12. Coke oven emissions	29. Propylene dichloride
13. 1,3-Dichloropropene	30. Quinoline
14. Diesel particulate matter	31. 1,1,2,2-Tetrachloroethane
15. Ethylene dibromide	32. TCE
16. Ethylene dichloride	33. VC
17. Ethylene oxide	

react with themselves and with oxygen in the air to generate additional toxicants. The formation of ozone is an example of such reactivity. Reactive organic molecules and nitrogen oxides react with atmospheric oxygen in the presence of sunlight via free-radical mechanisms to produce ozone and a large number of new toxicants.

7.4 Confined Air Pollutants

The consideration up to this point has been on pollutant molecules in the atmosphere. Air pollution, however, can also be hazardous in more confined areas, such as those found in outdoor areas with limited air circulation, in buildings, in rooms, and in other tight indoor areas with limited circulation. Confined air pollutants can be vapors, aerosols, or particles that are released into an area with limited air circulation. These releases can be from manufacturing, application of paints and adhesives, tobacco smoking, fires, paraffin wax candles burning, off-gassing of particle board and plywood used in construction, off-gassing of newly installed carpeting, application of cleaning products, pesticide use, and growth of mold and mildew. Often, the health effects observed in enclosed buildings are due to one or more of these releases but not identified with any one particular source. In such situations, the term “sick building syndrome” is often applied [6].

An example of air pollution in a confined space is the air in an airplane. The air in commercial airplanes contains reduced levels of oxygen, increased levels of carbon monoxide, carbon dioxide, ozone, VOCs, and particulate matter. These contaminants have led to cockpit crew, cabin crew, and passenger complaints of headache, fatigue, fever, and respiratory difficulties [7]. Another example of confined space air

pollution is when solvent fumes are generated when interior walls of buildings with inadequate air circulation are painted [8].

7.5 Air Pollution in the Breathing Zone

Air pollution can be limited to the breathing zone, i.e., the area within a short distance of the nose and mouth. Air pollution in the breathing zone generally does not impact others not in that zone. An example of breathing zone air pollution is that experienced by pathologists and histology technicians in (CNS and respiratory effects) preparing and microscopically examining slides prepared containing formaldehyde, toluene, and xylene. The health effects noted were headache, indigestion, memory disturbances, mood swings, loss of equilibrium and judgment, pulmonary functional impairment, upper respiratory irritation, eye irritation, and dermatological symptoms [9–11].

Another example of breathing zone air pollution is the use of theatrical fogs and smokes on stages and film sets. These are composed of aerosolized glycol ethers or mineral oil and are inhaled by actors during the course of their work. Health effects of such exposure include acute and chronic upper and lower respiratory ailments [12]. Theatrical fog and smoke aerosol exposure is not always limited to actors' breathing zones. When large quantities of these are used in theaters, a confined space exposure is established and audiences are also exposed.

7.6 Air Pollution and Health Risk

Using the industrial air pollution reports (toxic chemical air releases) that are reported to it by industry, EPA calculates a health risk score for each square kilometer of the United States. The health risk or probability that exposure to that particular air mass will induce illness is defined as the hazard multiplied by the exposure [13]:

$$\text{Health Risk} = \text{Hazard} \times \text{Exposure}$$

In calculating the hazards, EPA relies upon animal experiments and human studies for information to establish the probability of illness as a function of different exposure levels. The exposures used in the equation are derived from smokestack monitors strategically placed or from mathematical models that take meteorological factors into consideration. The paths taken by the pollution and numbers of males and females of different ages, who reside in each area, are taken into consideration in calculating health risk scores.

The health risk scores are not intended to measure the risks of being stricken by the exposures or the actual exposures to toxicants. Rather, they are meant to help screen for polluted areas that may need additional study. The health risk scores are also not definitive for the following three reasons:

1. The scores are based on the amount of toxic pollution released by each site (factory, mine, etc.) in the area. The data for the amounts considered are provided by the sites and are not independently gathered or quality controlled.

2. Scores are tied to the paths taken by the pollutants through the air. Wind condition, temperature, and relative humidity, however, vary widely, so the same amount of pollution can have far different effects on different days or even at different times of the same day. Breathing zone concentrations of pollutants can range from acceptable to extremely toxic in the same location as a function of time.
3. The health risk scores do not take other conditions and activities into consideration. The use of toxic chemicals for other purposes in an area is ignored. The following are examples of these:
 - a. Painting with alkyd paints introduces VOCs into the air.
 - b. Spraying pesticides onto farm land introduces these toxicants into the air.
 - c. Operating gasoline and diesel-powered vehicles introduces numerous hydrocarbons and particulates into the air.

7.7 Mixtures

The chemicals listed in Tables 7.1 and 7.2 contain numerous hydrophiles and lipophiles. The numbers of mixtures possible are impossible to calculate. When people are stricken following exposure to polluted air, health effects are often attributed to an inordinately high concentration of a particular toxicant. An example of such a situation is what occurred in Bhopal, India, in 1984 when a huge quantity of methyl isocyanate was released from a chemical plant. Such single chemical effects, however, are the exception, rather than the rule. Most polluted air contains complex mixtures of chemicals that often produce effects that cannot be attributed to the known toxicology of the individual species.

The toxicological effects of mixtures of air pollutants are not always ascribable to single chemicals. Some examples, however, of simple mixture effects are well known. Co-exposure to mixtures of carbon monoxide and carbon dioxide produces a synergistic effect, by increasing the degree of acidosis and extending the recovery time, compared with what is observed for the single chemicals. Simultaneous exposure to carbon dioxide and hydrogen cyanide increases the LC50 (amount of chemical that causes 50% of the test animals to die) of laboratory animals [14]. Air pollutant mixtures are often complex in phase as well as in diversity. Solid particles act as absorption sites for vapors, and liquids and aerosols act to introduce mixtures of different liquids. These are discussed in the following sections.

7.8 Particulate Matter

Particulate air pollutants arise from many sources, including natural ones. These include:

1. *Mining*: Mining operations, particularly surface mining, result in the release of particulates of the ore (or coal) which is being mined as well as particles of surrounding matter. The effects generally are localized, but when ultrafine particles are released they travel great distances [15–18].

2. *Agriculture*: Agricultural workers as well as non-agricultural residents of agricultural areas are exposed to organic dusts (from grain and animal waste) and toxic gases (ammonia and hydrogen sulfide). A significant percentage of these workers and residents suffer from respiratory diseases and syndromes, including chronic bronchitis and asthma-like syndrome [19, 20].
3. *Manufacturing*: Virtually all grinding operations result in the release of particulates to the air. Quarrying, cement manufacturing, smelting, pigment grinding, mixing of solids (e.g., silica or talc) into paints and adhesives are just a few examples [21].
4. *Fires*: Combustion of any kind produces toxic particulate matter, smoke. The combustion can be natural such as a lightning-induced forest fire or unnatural such as the burning of fossil fuel for energy production, a petroleum refinery, or plastics warehouse fire [22, 23]. In addition to particulates, fires produce PAHs, carbon monoxide, organic and inorganic cyanides, and free radicals that are toxic [24, 25].
5. *Tobacco smoke*: Tobacco smoke produces particulate matter that acts as an adsorption site for toxic vapors [26]. In addition to particulates, tobacco smoke produces more than 4000 individual toxic compounds, including 43 known carcinogens [27]. Many of the toxic effects of tobacco smoke that have been established empirically cannot be ascribed to individual compounds in that smoke. With more than 4000 different toxins, the number of mixtures possible is incalculable. Numerous examples of synergism between tobacco smoke and other toxicants have been identified. These include tobacco smoke and asbestos or other mineral fibers [28, 29], alcohol [30, 31], organic solvents [32], biological pathogens [33], and radon [34]. The toxicology of tobacco smoke will be addressed in detail in Chapter 15.
6. *Volcanoes*: Volcanoes are natural events that result in the release of huge quantities of particulates into the atmosphere [35]. On May 18, 1980, Mount St. Helens, in Washington State, erupted violently. Volcanic ash expelled during the eruption was of respirable size and resulted in a large number of respiratory injuries to those exposed [36].

Particulate matter in polluted air presents a mixture hazard that exceeds its own toxicology [37]. When lodged in the lungs particles can act as adsorption sites for inhaled vapors and mists. Carbon black is an example of such a particulate. Carbon readily adsorbs hydrocarbons, including PAHs, on its surface and retains these toxicants in the lungs for periods of time far exceeding their usual residence time. Asbestos, too, acts as an absorption site for other toxicants.

The aftermath of the World Trade Center fire and collapse is an example of the toxic effects of particulate matter. New York City firefighters and emergency response personnel who were exposed to dust from the collapse of the World Trade Center buildings following the September 11, 2001 attack have experienced a decrease in lung capacity [38].

7.9 Aerosols

Aerosols present dangers that far exceed those of vapors. Aerosols are small droplets of liquids suspended in air. Inhalation of these droplets into the lungs introduces very large quantities of toxicants relative to the inhalation of vapors of the same chemicals. By introducing the chemicals in liquid form, aerosols greatly facilitate the propensity for chemicals to induce chemical burns in lung tissue. Aerosols also greatly

facilitate the absorption of mixtures by respiratory tract tissues. Aerosolized cleaners containing mixtures of ammonia and glycol ethers are far more irritating to the respiratory tract than the vapors of these chemicals alone because the mixture, inhaled as a liquid, introduces much greater quantities of this irritant mixture into the lungs.

Sulfur and nitrogen oxides react in the atmosphere to produce sulfuric and nitric acid, respectively. These react with photochemical products and airborne particles under ambient conditions to produce acid aerosols. Mixtures of these acid aerosols and ozone are synergistic and cause respiratory effects that are significantly more severe than those of ozone or the acids alone [39–41].

7.10 Effects of Nonspecific Origin

Short-term exposure to air pollution has been known as a cause of chronic obstructive pulmonary disease (COPD) for some time. Recently, however, it has been shown that long-term exposure to traffic-related air pollution contributes to COPD as well [42]. Traffic-related air pollution includes PAHs and particulate matter. This finding demonstrates the need to limit exposures to toxic chemicals wherever possible when endpoints remain unknown.

7.11 Summary

Air pollution results in the uptake of large numbers of chemicals of widely differing chemical and toxicological properties. When mixtures are inhaled (as is the case almost constantly) toxicological impacts that are not predicted from the known properties of the individual pollutants may ensue. This is particularly so when at least one of the chemicals is lipophilic and one is hydrophilic.

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8 Water Pollution

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8.1 Introduction

There are virtually no sources of drinking water on earth that are not contaminated with xenobiotics. Rainwater cleanses the atmosphere as it forms and falls. As a result, it contains dissolved acids, organic compounds, and heavy metals such as mercury and selenium in many areas. Surface collection basins from which potable water is drawn—rivers, streams, and lakes—accumulate ground level pollutants in addition to those carried in rainwater. Underground water, which is somewhat filtered and generally contains lesser quantities of pollutants than surface water, may itself be contaminated by ground releases of toxicants and by contaminants produced by chemical reactions in the soil and water.

Water intended for human consumption that is biologically contaminated is treated to remove bacteria, viruses, fungi, and parasites, by aeration, chlorination, ozone, ultraviolet radiation, or a combination of these methods. In the process of purification, decontamination by-products (DBPs) are produced. These are chemicals that are themselves toxic. DBPs will be discussed in Section 8.9.

Major sources of water pollutants include mining, manufacturing, farming, power production, and runoff from urban and suburban sprawl. Water pollution from each of these sources is discussed in the following sections.

8.2 Mining

Mining activities frequently impact water resources and contaminate surface water and groundwater systems. This is illustrated by the following examples.

1. Coal mining has widespread environmental impact. Coal mining discharges are acidic and some contain high concentrations of dissolved metals that are reflective of the mineral content of the coal. Surface coal mining (strip mining) is particularly toxic, for not only does it cause the release of acid and toxic compounds into streams and rivers, but it is also accompanied by the removal of top soil, thus preventing revegetation. This, in turn, results in the further runoff of pollutants into water systems and increases the toxic load of the water [1, 2]. In a typical example, the Deckers Creek watershed in northern West Virginia, coal mining has raised the acidity level and introduced high levels of calcium, iron, aluminum, manganese, and zinc over a 25-year period. The water quality of the system continued its degradation even after mining ceased due to runoff from an abandoned underground mining complex [3].
2. The mining and smelting of metal ores produce large quantities of waste because the metal that is mined and refined is only a small fraction of the total material mined. Copper mining produces large amounts of mine wastes and tailings. Cobalt smelting produces approximately 0.11 mg of sulfur per milligram of cobalt produced. Zinc and lead smelting results in the release of large quantities of cadmium and lead into the environment. Gold and other metals are often found in ores where metals are present as sulfides such as pyrite (FeS_2) and arsenopyrite (FeAsS). When these ores are exposed to air during mining activities the sulfides are oxidized to produce acidified water that can typically have a pH of less than 2. The acidified water dissolves and mobilizes the metals and further pollutes the water environment. Such releases pollute surface waters and soil, and ultimately result in the uptake of heavy metal contaminants by humans [4].

3. In some areas, gold mining is accompanied by an amalgamation process using mercury. As a result humans are exposed to large quantities of mercury in such areas through uptake of contaminated water. In the Wau-Bulolo area of eastern Papua New Guinea, people living downstream of the gold mining area were found to have significantly higher levels of mercury in their hair than those living upstream of the mine [5].
4. Uranium has been mined extensively in Karnes County, Texas, for more than 30 years. Soil and drinking water wells have been shown to be contaminated with uranium-238 and thorium-232. Residents living near the mines have increased chromosomal aberrations and reduced DNA repair capacity [6].
5. Arsenic, a well-known skin carcinogen, coexists with tin in some tin-mining areas. In one tin-mining area in Malaysia, well water in the tin-mining area has been found to have high levels of arsenic and an association between living in the tin-mining area and development of skin cancer has been demonstrated [7].

8.3 Manufacturing

Steel and other metal processing plants, food processing plants, textile manufacturing plants, and chemical manufacturing plants are but a few of the numerous industrial operations that are point sources of toxicants to the aquatic environment. It can be safely said that quantities of all chemicals used in manufacturing are released into the environment. Though many chemicals are released to the ground and air environments, virtually all find their way into surface water and groundwater. Water percolating through soil carries toxic chemicals to groundwater. Runoff carries toxicants to surface water. Airborne chemicals and their reactants rain down and wash down with rainwater to surface bodies of water. It is beyond the scope of this book to examine the water pollution effects of manufacturing. Pulp and paper processing is an illustrative example of water pollution resulting from manufacturing.

The conversion of wood to fiber produces hundreds of chemical compounds that are discharged to surface water in effluents [8]. Processes which use chlorine to bleach pulp produce substantial quantities of toxic chlorinated organic compounds, including dioxins and furans [9], compounds which attack the respiratory, musculoskeletal, reproductive, and central nervous systems, skin, liver, and kidneys. These compounds are considered human carcinogens [10].

8.4 Farming

Farming is responsible for the release of four categories of water pollutants into the water environment. These are:

1. Silts
2. Pathogens
3. Nutrients
4. Pesticides.

Though the quantities of each pollutant that is released vary with farming practices and animals or crops raised, they are the most important nonpoint source of water pollution.

8.4.1 *Silts*

Silt formation associated with surface runoff has historically been the greatest agricultural pollutant. It has resulted not only in the loss of huge quantities of rich top soil, but also in the altering of water clarity (and associated changes in light penetration that greatly impact plant and animal life) and the binding and transport of toxic lipophilic chemicals in the water column. Lipophiles such as PCBs, mirex, kepone, and other pesticides are essentially insoluble in water. Their apparent solubility in water is due to their binding to lipophilic sites in silt. Such binding contributes to elevated levels of these toxicants in water by preventing evaporation and photolysis [11, 12].

8.4.2 *Pathogens*

Agricultural specialization has resulted in the concentration of large numbers of animals in relatively small areas. The amounts of manure produced per unit area often far exceed the abilities of the surrounding lands to assimilate these quantities. This is particularly the case with cattle feed lots and indoor poultry and pig systems. Runoff from these areas results in the introduction of significant quantities of pathogens to adjacent waters. It is quite common for drinking water wells in agricultural areas to exceed the allowable water quality standards for total coliform and fecal coliform [13]. There are significant health concerns associated with agricultural release of pathogens. Addressing these is beyond the scope of this book. The reader is referred to a monograph, however, for a good discussion of the subject [14].

8.4.3 *Nutrients*

Animal wastes and chemical fertilizers are applied to soil to provide the nitrogen, phosphorus, and trace elements necessary for crop growth. When applied, these fertilizers are either taken up by crops, remain in the soil, or enter the aquatic environments via leaching, runoff, and atmospheric transport of dusts.

Nitrogen is generally applied in the form of nitrate and phosphorus in the form of phosphate. Together, these contribute to the eutrophication of water, with algal blooms and greatly accelerated water plant growth. Increases in the bloom of blue green algae can result in an increase of natural toxins that pose risks to human health [9]. Though phosphate in drinking water does not by itself pose a significant risk to human health, nitrate does. High levels of nitrate in drinking water pose a threat of nitrate toxicosis or methemoglobinemia (oxygen starvation) [9]. A positive correlation between nitrogen compounds coming from fertilizer in farming and esophageal cancer has been found [15]. Mixtures of nitrate with the pesticides aldicarb or atrazine at levels found in the drinking water of farming communities are toxic to the immune, endocrine, and nervous systems [16].

Household lawn and garden use of fertilizers is small compared to farming usage. Runoff from home uses, however, leads to the introduction of significant quantities of nitrate and phosphate in surface and deep well drinking water sources in some areas.

8.4.4 Pesticides

Agricultural use accounts for about 80% of pesticides use. Agricultural pesticides can enter surface water and groundwater. These include accidental spills, atmospheric transport following volatilization, spray drift during application to crops, overspray, runoff from fields, disposal of pesticide product containers, and leaching of soluble pesticides through soil into underground aquifers [9]. Pesticides are relatively nonreactive either dissolved or suspended in water and may persist for many years [12, 17].

Herbicides are applied to roadways and railroad rights-of-way to control weeds and other plant life for safety and fire prevention purposes. Though arsenic herbicides were used for more than half of the twentieth century, these have been largely replaced by 2,4-D, triclopyr, and picloram. These herbicides have been found in wells adjacent to the application points [9].

Pesticides and herbicides are also applied directly to surface water for the control of insects, algae, and invasive weeds. 2,4-D, glyphosate, and copper sulfate are the pesticides most commonly applied to surface water [9].

Though household use of pesticides is small compared to farming stage, pesticides runoff does contribute to significant local contamination of drinking water in many areas.

The human toxicology of pesticides and pesticide mixtures will be examined in detail in Chapter 14.

8.5 Power Production

Power production is responsible for the introduction of toxic chemicals into drinking water via several routes. These include petroleum production (drilling, pumping, transport, and refining), coal mining, petroleum combustion, and coal combustion. Nuclear reactors that produce electricity also pollute the water environment through the introduction of massive quantities of heat to surface waters.

8.5.1 Petroleum Production and Refining

Drilling, pumping, and transporting of crude oil invariably results in some spills of petroleum. These spills result in the introduction of aliphatic, aromatic, and PAHs into surface water and groundwater. Many of the chemicals on EPA's list of 129 priority water pollutants (see Section 8.8) thereby enter drinking water sources.

Petroleum refineries generate large quantities of discharged wastewater. Refinery wastewaters contain numerous organic and metallic toxicants. These include aliphatic hydrocarbons, aromatic hydrocarbons (including benzene), PAHs, phenols, sulfides, amines, carbonyl compounds, and heavy metals [18, 19]. Petroleum refinery waste dumps contain numerous carcinogens, including benzene, and runoff from these dumps contaminates nearby drinking water sources. Benzene can be absorbed through the skin upon contact with water containing benzene, thus increasing the risk of leukemia in those so exposed [20]. A correlation between residing in proximity to petroleum waste dumps (from which runoff into drinking water sources occurs) and increased incidence of leukemia has been reported [21].

8.5.2 Coal Mining

Coal mining is a major source of aquatic environment pollutants. This was discussed earlier in Section 8.2.

8.5.3 Petroleum Use and Combustion

Combustion of petroleum products produces airborne aliphatic hydrocarbons, aromatic hydrocarbons, PAHs, aldehydes, ketones, metals, and sulfur dioxide [22]. These airborne chemicals ultimately settle or are brought down by rain onto surface waters and onto the ground, from where they run off into surface waters. The actual combustion products produced vary by petroleum source. The use of different grades of fuel oil, diesel, and gasoline lead to different pollutants. Methyl *tert*-butyl ether (MTBE) has been added (as a replacement for lead) to gasoline to improve combustion efficiency since 1978. Its wide-scale use has led to it becoming a prevalent groundwater contaminant worldwide [23]. Similarly, PAHs from petroleum usage are now major water polluters worldwide and are found in marine life [24].

8.5.4 Coal Combustion

Combustion of coal produces many of the same ultimate water pollutants as combustion of petroleum does, i.e., PAHs. Coal burning, however, produces greater quantities of metals, sulfur dioxide, and haloacids. Coal combustion stack emissions contain significant quantities of arsenic, mercury, selenium, copper, and tin [25]. Sulfur dioxide is ultimately converted to sulfuric acid in the air. Sulfuric acid and the haloacids (HF, HCl, HBr, and HI) ultimately come down as acid rains and acidify surface waters [26]. Acidified water is by itself toxic to marine life. Its effect is amplified, however, by the solubilization of metals and hydrolysis of other chemical compounds.

8.5.5 Cooling Towers

Cooling towers are used in many industrial areas to cool water that is required to remove excess heat produced by fuel combustion or other reactivity. Nowhere is more cooling water used than in the production of electricity from nuclear fission. In virtually every cooling tower application, cool water is taken from a surface source (river, estuary, or lake) and returned to its source heated up. The introduction of warm water to its source disrupts marine plant and animal life and also catalyzes chemical reactions. These have the effect of increasing concentrations of toxic chemicals in water that is often taken up for drinking water use downstream [9].

8.6 Urban Runoff

Urban runoff is the greatest cause of surface water pollution in many parts of the world. Toxins contained in runoff include pathogens, nutrients (nitrate and phosphate),

hydrocarbons (including PAHs), pesticides, and heavy metals (including Cd, Cu, Cr, Pb, Zn, and Fe) [27–31]. Urban runoff is particularly troublesome where storm water runoff is untreated and enters rivers and lakes from which drinking water is drawn. In areas where storm water runoff is commingled with household sewage for treatment, heavy runoff often overwhelms treatment plants and results in the release of raw sewage into the aquatic environment.

8.7 Home and Personal Care Products

Household use of chemicals and chemical products is ultimately a major source of contamination of drinking water in the United States. EPA has identified 13 major categories of water pollutants in this area [32]. The list and a discussion of each item follows:

1. Cleaners
2. Cosmetics
3. Deodorizers
4. Disinfectants
5. House and garden pesticides
6. Laundry products
7. Medicines
8. Ointments
9. Paint and paint products
10. Photographic chemicals
11. Polish
12. Preservatives
13. Soaps.

8.7.1 *Cleaners*

Cleaning products are used regularly in most households. These include dishwashing detergents, denture cleaners, toilet bowl cleaners, oven cleaners, drain cleaners, wood and metal cleaners and polishes, tub, tile, and shower cleaners, bleach and pool chemicals. Toxic chemicals contained in household cleaners include ammonia, chlorine, glycol ethers, aliphatic hydrocarbons, aromatic hydrocarbons, chlorinated hydrocarbons, surfactants, and heavy metals [32].

8.7.2 *Cosmetics*

Cosmetics are used daily in most households. These include facial and body creams, hair colorants, setting and other treatment products, nail polishes, lipsticks, facial powders, perfumes, and deodorants. Toxic chemicals contained in cosmetics include many of those listed on the EPA 129 priority pollutant list (see Section 8.8). Some of these are formaldehyde, PAHs, aliphatic and aromatic hydrocarbons, and heavy metals [32].

8.7.3 *Deodorizers*

Deodorizers are used in bathrooms, around pets, on carpets and upholstery, and for esthetic purposes. Toxic chemicals contained in deodorizers include glycol ethers, quaternary ammonium compounds, aromatic and aliphatic hydrocarbons, alcohols, aldehydes, and esters [33].

8.7.4 *Disinfectants*

Disinfectants are used in bathrooms and kitchens to combat mold and mildew. Toxic chemicals contained in these include chlorine, chloramines and quaternary ammonium compounds, alcohols, and glycol ethers [32].

8.7.5 *House and Garden Pesticides*

Pesticides used around the house and garden include insecticides, herbicides, rodenticides, fungicides, and fumigants. Toxic chemicals contained in pesticides include organochlorine and organophosphate compounds, carbamates, and arsenicals. The solvents used as carriers for these include aliphatic and aromatic hydrocarbons, alcohols, and glycol ethers [34].

8.7.6 *Laundry Products*

Laundry washing consumes and releases large amounts of chemicals into wastewater. Laundry products used in the household include detergents, bleaches, builders, and metal chelating agents. Toxic chemicals contained in these include surfactants, chlorine, organic peroxides, phosphates, alkalis, and glycol ethers [35].

8.7.7 *Medicines*

Medicines contain antibiotics and other biologically active chemicals which help humans fight disease. As stated at the outset, this book will not address pharmaceutical products and their toxic effects. Medicines, however, contain inactive components called excipients, substances added to confer consistency or form to a drug, preservatives, stabilizers, sweeteners, and colorants. These additives frequently make up the majority of the drug product. They are considered inert and intended to affect the therapeutic action of the drug. Almost 800 chemicals in this category have been approved by the U.S. Food and Drug Administration (FDA) for use as inactive ingredients in pharmaceuticals. Many of the chemicals used as excipients are themselves toxic and these contaminate water when introduced into it [36].

A few examples of excipients and their toxic effects are:

Benzalkonium chloride	Bronchospasm [37]
Aspartame	Headache and seizure [38]
Azo dyes (food colors)	Hyperactivity [38]
Sulfites	Anaphylaxis [39]
Propylene glycol	Skin eruptions [37–39]

Table 8.1 Major Cities and Areas in the United States with Drinking Water Contaminated by Pharmaceuticals

Arlington, TX	Milwaukee, WI
Atlanta, GA	Minneapolis, MN
Cincinnati, OH	New Orleans, LA
Columbus, OH	Northern NJ
Concord, CA	Philadelphia, PA
Denver, CO	Portland, OR
Detroit, MI	Riverside County, CA
Indianapolis, IN	San Diego, CA
Las Vegas, NV	San Francisco, CA
Long Beach, CA	Southern CA
Los Angeles, CA	Tucson, AZ
Louisville, KY	Washington, DC

Many of the chemical water pollutants released by household products are identical to those released through industrial and agricultural activities. Though the quantities of pollutants released as a result of industrial and agricultural use are generally far greater than the quantities resulting from household use, in some instances household usage bears primary responsibility for localized drinking water contamination by toxic chemicals. This is particularly so when the discharges from municipal wastewater treatment plants or household septic systems enter downstream drinking water uptakes, as is often the case [40]. Though this book does not address the toxicology of pharmaceutical products, it is worth noting that in a study of the drinking water supplies of major cities and areas in the United States, 24 of these were found to contain prescription drugs in their water. Philadelphia alone contained 56 different drugs in its drinking water. These include amoxicillin, azithromycin, carbamazepine, diclofenac prednisone, and tetracycline [41]. The list of major cities and areas with drinking water contaminated by pharmaceuticals is listed in Table 8.1.

8.7.8 Ointments

Medical ointments are applied topically to various body parts. Significant quantities of these are washed down the drain via bathing and hand washing following application. Toxic chemicals contained in these include aromatic hydrocarbons, chlorinated hydrocarbons, and heavy metals [32].

8.7.9 Paint and Paint Products

Most paints used in the household today are water-based products. Significant quantities of paints, primers, and brush cleaners are washed down the drain during cleanup following painting. Water-based paints contain numerous toxic chemicals. These include pigments (many with heavy metals), biocides, glycol ethers, binders,

amines, acrylate and other polymer monomers, surfactants, aliphatic and aromatic hydrocarbons, alcohols, ketones, and esters [42, 43].

8.7.10 Photographic Chemicals

Many photographers who develop their own pictures pour spent solutions down the drain. Toxic chemicals released this way include acetic acid, aminophenol, ammonium hydroxide, diethanolamine, silver, sodium thiosulfate, and more than 80 others [44, 45].

8.7.11 Polishes

Polishes encompass a broad spectrum of products, including furniture polishes, shoe polishes, floor waxes, and metal polishes. Many of these are water-based products and cleanup entails washing with water that is poured down the drain. Toxic chemicals contained in these products and released to wastewater include chlorinated hydrocarbons, acrylates, surfactants, preservatives (including formaldehyde), glycol ethers, silver, and phthalates [32].

8.7.12 Preservatives

Many cosmetics, paints, ointments, foods, shampoos, and medicines contain preservatives to combat biological degradation. Toxic chemicals used as preservatives include mercury compounds, formaldehyde, methyl and propyl *p*-aminobenzoic acids (PABAs), butylated hydroxyanisole (BHA), BHT, benzoic acid, and quaternary ammonium compounds [32].

8.7.13 Soaps

Soaps are used in virtually every household every day. Basic soap is produced by the saponification (hydrolysis with sodium hydroxide) of animal or vegetable fats and has little toxicity. Soaps commonly used, however, contain additives to give them deodorant and antimicrobial properties. Such soaps may contain chloroxylenol, phenol, triclosan, methylisothiazolinone (MIT), and other toxicants which are released to water streams [46].

8.8 Priority Water Pollutants

In 1979, the U.S. EPA published a list of 129 priority water pollutants from human activities most responsible for the contamination of water [47]. Table 8.2 lists these chemicals as well as their sources.

Since this priority list was first drawn up in 1979, many other hazardous contaminants in water have been identified. These are addressed in the next section.

Table 8.2 EPA 129 Priority Pollutants and Their Product Sources

Priority Pollutant	Source
1. Acenaphthene	Manufacturing of insecticides, fungicides, dyes, plastics
2. Acrolein	Chemical manufacturing, intermediate
3. Acrylonitrile	Chemical manufacturing
4. Benzene	Organic chemicals, solvents, petroleum products
5. Benzidine	Manufacturing of chemicals, rubber, and dyes
6. Carbon tetrachloride	Manufacture of chlorinated hydrocarbons, chemical intermediate
7. Chlorobenzene	Chemical manufacturing, degreaser
8. 1,2,4-Trichlorobenzene	Manufacturing of chemicals, heat transfer lubricant
9. Hexachlorobenzene	Fungicide for wood preservation
10. 1,2-Dichloroethane	Cleaners and wax removers
11. 1,1,1-TCA	Degreasers, cleaners
12. Hexachloroethane	Insecticides
13. 1,1-Dichloroethane	Degreasers
14. 1,1,2-TCA	Waxes, cleaners, photographic products
15. 1,1,2,2-Tetrachloroethane	Fumigant, garden sprays
16. Chloroethane	Waxes, cleaners
17. Bis(chloromethyl) ether	Chemical manufacturing
18. Bis(2-chloroethyl) ether	Paints, varnishes, callus removers
19. 2-Chloroethyl vinyl ether	Waterproofing compounds
20. 2-Chloronaphthalene	Engine oil additive
21. 2,4,6-Trichlorophenol	Adhesives, cleaners, disinfectants
22. <i>p</i> -Chloro- <i>m</i> -cresol	Glue, paint and shampoo preservatives
23. Chloroform	Manufacturing solvents, DBP
24. 2-Chlorophenol	Disinfectants, cleaners, paints
25. 1,2-Dichlorobenzene	Waxes, polishes, cleaners, deodorizers, preservatives
26. 1,3-Dichlorobenzene	Waxes, polishes, cleaners, deodorizers, preservatives
27. 1,4-Dichlorobenzene	Fruit spray, household cleaners, dyes, disinfectants
28. 3,3-Dichlorobenzidine	Dye manufacture
29. 1,1-DCE	Plasticizer, environmental decomposition of TCE
30. 1,2-DCE	Solvents, cleaners
31. 2,4-Dichlorophenol	Wood preservatives, insect repellants cosmetics
32. 1,2-Dichloropropane	Tar removers, waxes, degreasers
33. 1,3-Dichloropropylene	Tar removers, waxes, degreasers
34. 2,4-Dimethylphenol	Asphalt products, shampoos, skin treatments
35. 2,4-Dinitrotoluene	Manufacture of TNT
36. 2,6-Dinitrotoluene	Manufacture of TNT
37. 1,2-Diphenylhydrazine	Manufacture of chemicals
38. Ethylbenzene	Solvents, manufacture of plastics, petroleum fuels
39. Fluoranthene	Coal tars, antibiotic creams, shampoos, skin treatments
40. 4-Chlorophenyl phenyl ether	Dielectric fluid
41. 4-Bromophenyl phenyl ether	Dielectric fluid
42. Bis(2-chloroisopropyl) ether	Waxes, paint removers, degreasers
43. Bis(2-chloroethoxy) methane	Manufacture of adhesives, sealants
44. Methylene chloride	Solvents, degreasers, cleaners
45. Methyl chloride	Manufacture of chemicals and herbicides
46. Methyl bromide	Manufacture of crop fumigants
47. Bromoform	Solvents, manufacture of pharmaceuticals, DBP

(Continued)

Table 8.2 (Continued)

Priority Pollutant	Source
48. Dichlorobromomethane	Drinking water treatments, waxes, greases
49. Trichlorofluoromethane	Aerosol propellants, perfumes, deodorants
50. Dichlorodifluoromethane	Aerosol propellants, perfumes, deodorants
51. Chlorodibromomethane	Aerosol propellants, perfumes, deodorants, fire extinguishers
52. Hexachlorobutadiene	By-product of TCE manufacturing
53. Hexachlorocyclopentadiene	Pesticide manufacture
54. Isophorone	Solvents, pesticide manufacture, degreasers
55. Naphthalene	Deodorants, detergents, moth repellent, skin treatments
56. Nitrobenzene	Textiles, dyes
57. Nitrophenol	Manufacture of dyes and chemicals
58. 4-Nitrophenol	Pesticide manufacture
59. 2,4-Dinitrophenol	Manufacture of pesticides, photographic products
60. 4,6-Dinitro- <i>o</i> -cresol	Pesticides
61. <i>N</i> -Nitrosodimethylamine	Manufacture of dyes
62. <i>N</i> -Nitrosodiphenylamine	Manufacture of rubber
63. <i>N</i> -Nitrosodi- <i>N</i> -propylamine	Manufacture of organic chemicals
64. Petachlorophenol	Wood preservatives
65. <i>n</i> -Phenol	Adhesives, preservatives, disinfectants, callus removers
66. Bis(2-ethylhexyl)phthalate	Plasticizer
67. Butylbenzylphthalate	Plasticizer
68. Di- <i>n</i> -butylphthalate	Plasticizer
69. Dioctylphthalate	Plasticizer
70. Diethylphthalate	Plasticizer
71. Dimethylphthalate	Plasticizer
72. Benzo[a]anthracene	Cigarette smoke, asphalt products, petroleum combustion
73. Benzo[a]pyrene	Cigarette smoke, asphalt products, petroleum combustion
74. 3,4-Benzofluoranthene	Cigarette smoke, asphalt products, petroleum combustion
75. 11,12-Benzofluoranthene	Cigarette smoke, asphalt products, petroleum combustion
76. Chrysene	Cigarette smoke, asphalt products, petroleum combustion
77. Acenaphthylene	Dye manufacturing, petroleum combustion
78. Anthracene	Dye manufacturing, petroleum combustion
79. Benzo[c]perylene	Dye manufacturing, petroleum combustion
80. Phenanthrene	Dye manufacturing, petroleum combustion
81. Indeno[1,2,3- <i>cd</i>]pyrene	Dye manufacturing, petroleum combustion
82. Dibenzo[a,h]anthracene	Dye manufacturing, petroleum combustion
83. Indeno[1,2,3- <i>cd</i>]pyrene	Dye manufacturing, petroleum combustion
84. Pyrene	Dye manufacturing, petroleum combustion
85. Tetrachloroethylene	Dry cleaning solvent, degreasers
86. Toluene	Solvents, adhesives, paints, varnishes
87. TCE	Degreasers, solvents

(Continued)

Table 8.2 (Continued)

Priority Pollutant	Source
88. VC	Manufacture of PVC resins, adhesives, environmental decomposition of TCE
89. Aldrin	Insecticides
90. Dieldrin	Insecticides
91. Chlordane	Insecticides
92. 4,4'-DDT	Insecticides
93. 4,4'-DDE	Environmental decomposition of 4,4'-DDT
94. 4,4'-DDD	Impurity in 4,4'-DDT
95. Endosulfan-alpha	Acaricides
96. Endosulfan-beta	Acaricides
97. Endosulfan sulfate	Acaricides
98. Endrin	Insecticides, rodenticides
99. Endrin aldehyde	Insecticides, rodenticides
100. Heptachlor	Insecticides, rodenticides
101. Heptachlor epoxide	Insecticides, rodenticides
102. BHC-alpha	Insecticide, fungicide
103. BHC-beta	Insecticide, fungicide
104. BHC-gamma	Insecticide, fungicide
105. BHC-delta	Insecticide, fungicide
106. TCDD	Manufacture of chlorophenols, herbicide contaminant, incineration of chemical wastes
107. Toxaphene	Insecticides
108. Arochlor 1016	Electrical transformers, carbonless copy papers
109. Arochlor 1221	Electrical transformers, carbonless copy papers
110. Arochlor 1232	Electrical transformers, carbonless copy papers
111. Arochlor 1242	Electrical transformers, carbonless copy papers
112. Arochlor 1248	Electrical transformers, carbonless copy papers
113. Arochlor 1254	Electrical transformers, carbonless copy papers
114. Arochlor 1260	Electrical transformers, carbonless copy papers
115. Antimony	Mining, smelting, paints, fireproofing compounds
116. Arsenic	Insecticides, herbicides, pressure-treated woods
117. Asbestos	Construction materials, insulation materials
118. Beryllium	Electrical components, manufacturing of chemicals
119. Cadmium	Welding rods, alkaline storage batteries, fluorescent lamps
120. Chromium	Chrome plating, paints, chemical manufacturing
121. Copper	Corrosion in plumbing, algicides, bronze plating
122. Cyanide	Ore refining, combustion of plastics, electroplating
123. Lead	Corrosion in plumbing, paints applied pre-1973, storage batteries
124. Mercury	Electrical switches, pharmaceutical preservatives, mining of gold and silver
125. Nickel	Mining, smelting, alloy production
126. Selenium	Mining, coal combustion, glass manufacture
127. Silver	Dentistry, photographic film, jewelry
128. Thallium	Smelting and refining of lead and zinc, pesticides
129. Zinc	Textile finishing, skin treatments, electrical batteries

8.9 Chemical Reactions in Water

8.9.1 Groundwater

In addition to those chemicals released directly, chemical reactions in the environment generate still more pollutants. After being discharged onto soil and into groundwater, some pollutants are degraded into chemicals that are sometimes more toxic than the parent compounds. Such degradation occurs via chemical oxidation, reduction, hydration, and bacterial action.

The transformations of the chlorinated hydrocarbons perchloroethylene (PCE), trichloroethylene (TCE), and 1,1,1-trichloroethane are illustrative of these types of reactions. *Cis*- and *trans*-1,2-dichloroethylene (1,2-DCE), 1,1-dichloroethylene (1,1-DCE), and VC are often found in well water which has been contaminated only with tetrachloroethylene and/or TCE [48]. Some of the transformations of PCE and TCE are biologically catalyzed and occur in soil and sediment, while others are believed to occur in groundwater [49, 50]. 1,1,1-Trichloroethane hydrolyzes to 1,1-DCE in groundwater [51]. Figure 8.1 shows the degradation sequence of tetrachloroethylene and TCE.

Whatever the nature of the degradation, the discharge of chlorinated hydrocarbon solvents results in the formation of the highly toxic degradation products DCE and VC. DCE irritates the eyes, skin, and respiratory tract and depresses the central nervous system [52]. 1,1-DCE is a suspected human carcinogen [53]. VC may cause scleroderma, a disease that causes skin to become smooth, tight, and shiny and causes the bones in the fingers to erode. Repeated exposure can damage the liver, kidneys, CNS, and blood cells. VC is a known liver carcinogen [54]. Such transformations help shed light on how some of the “mysterious” human illnesses and cancers are triggered by the discharge of pollutants into water that are not by themselves highly toxic.

8.9.2 Disinfection By-Products

Drinking water has been disinfected with chlorine for approximately 100 years to protect against waterborne infectious diseases. In addition to chlorination, other methods of drinking water disinfection include the use of chlorine dioxide (either alone or in combination with chlorine), the addition of ammonia to chlorine to form chloramines, ozone treatment, oxidation with potassium permanganate, and ultra-violet radiation. Chlorination, however, is by far the most widely used method. Treatment with chlorine has virtually eliminated cholera, typhoid, dysentery, hepatitis A, and other waterborne diseases [55].

Chlorine may be injected into water as elemental chlorine, hypochlorous acid, or hypochlorite (depending upon pH). An advantage of using chlorine is that it maintains a residual level throughout the distribution system, thereby preventing regrowth of micro-organisms before reaching end users.

It was discovered in the 1970s that chlorination of raw water high in organic content and/or infused with sea water results not only in the disinfection of water,

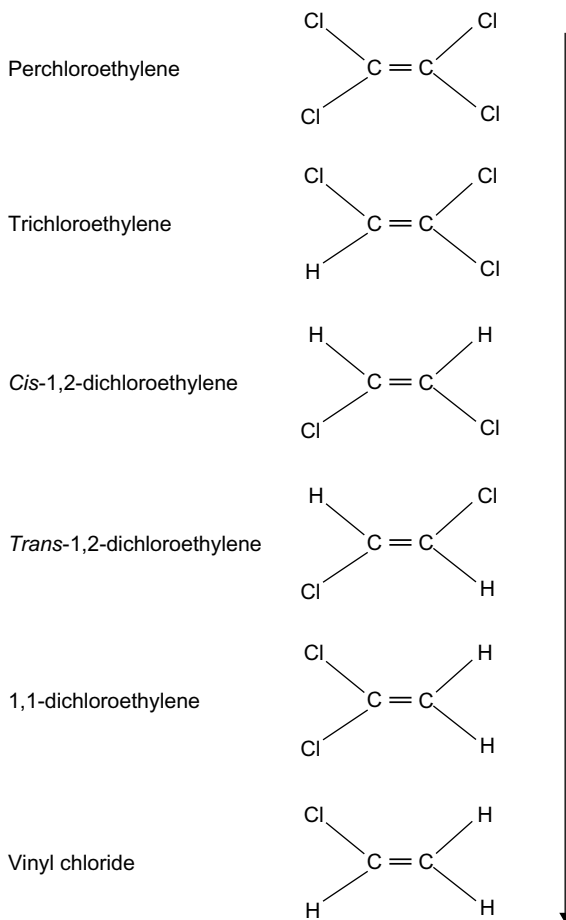


Figure 8.1 The degradation sequence of tetrachloroethylene and TCE.

but also in the formation of disinfection by-products (DBPs). These include trihalo-methanes (THMs), haloacetic acids (HAAs), and haloacetonitriles (HANs) [56, 57]. These chemicals are individually toxic at high concentrations and can cause cancer, liver disease, kidney disease, birth defects, and reproductive failures [58–60, 82, 83].

THM MCL in drinking water is regulated by EPA under the Safe Drinking Water Act [61]. EPA does not set limits on the individual THMs (chloroform, bromoform, bromodichloromethane, and chlorodibromomethane), but limits the total trihalo-methane (TTHM) concentration to 100 ppb. In the 1990s it was found that drinking water contaminated with TTHMs at concentrations below the EPA allowable MCL of 100 ppb cause spontaneous abortion in humans [62]. No one THM shows such toxicity at these low concentrations. The study that reported this phenomenon and others like it, however, did not report on the concentrations of other DBPs (HAAs

and HANs) in the water consumed, though these are almost always present in chlorinated drinking water containing THMs.

A study reported in 2006 covering spontaneous abortions in three different locations in the United States reported somewhat contradictory findings. The study did not find a correlation between drinking five or more glasses of water high in TTHMs (>75 ppb) and increased incidences of spontaneous abortion in all areas examined. This study, too, did not report on the concentration of other DBPs individually but did consider ingested total organic halide (total DBP). The study found sporadic elevations in pregnancy loss, most notably when ingested total organic halides were high [63].

DBPs contain numerous lipophiles and hydrophiles. The K_{ow} values for the four THMs are:

Chloroform	1.97
Bromoform	2.40
Chlorodibromomethane	2.16
Bromodichloromethane	2.00

As can be seen from these data, all four THMs are of similar lipophilicity. Individually and together they will facilitate the absorption of hydrophiles dissolved in them. Drinking water contains hundreds of dissolved chemicals in addition to DBPs. It is believed that the spontaneous abortions observed are due to a lipophilic/hydrophilic chemical mixture of DBPs and/or other dissolved chemicals of unknown composition [64].

8.10 Drinking Water Contaminants in the United States

The results of human activities described in the previous sections of this chapter have resulted in the release of thousands of pollutants into the environment. In a good portion of the world, groundwater and surface water are treated to disinfect biological agents and remove chemical pollutants prior to human consumption. Despite such treatment, the water consumed by almost all of the world's population is contaminated with chemical toxicants. In the United States, tap water tests from 1998 through 2003 on more than 39,000 water systems in 42 states, serving more than 231 million people, detected 260 different pollutants. These are characterized by their sources in Tables 8.1 through Tables 8.7. The data that follow in these tables as well as those in Table 8.6 were compiled and reported by the Environmental Working Group [65]:

- Table 8.3—Agricultural pollutants from pesticides, fertilizers, and factory farms (82 chemicals).
- Table 8.4—Sprawl and urban pollutants from road runoff, lawn pesticides, and human waste (58 chemicals).
- Table 8.5—Industrial pollutants (166 chemicals).
- Table 8.6—Water treatment and distribution by-products (43 chemicals).
- Table 8.7—Naturally occurring, but in higher concentrations than naturally present due to agriculture, sprawl or industrial activities (40 chemicals).

Table 8.3 Agricultural Pollutants in U.S. Drinking Water

Ammonia	Trifluralin
Chlorate	Ethion
Nitrate and nitrite mix	Heptachlor
Nitrate (alone)	3-Hydroxycarbofuran
Nitrite (alone)	Heptachlor epoxide
Phosphate	Endosulfan I
Sulfate	Dieldrin
Thallium	DDT
Methylene blue active substances (MBAS) (surfactants)	Butachlor
Phosphorus	Propachlor
Endrin	Bromacil
Desethylatrazine	Dacthal
Deisopropylatrazine	Diuron
Lindane	2,4-D
Methoxychlor	2,4-DB
Toxaphene	2,4,5-TP (Silvex)
Carbaryl	2,4,5-T
Methomyl	Chloramben
Baygon (Propoxur)	Dichlorprop
Methiocarb	Bromomethane
Acetochlor	Isophorone
Paraquat	Alpha-lindane
Prometon	Beta-lindane
2,4-bis-6-(isopropylamino)-1,3,5-triazine	Aldrin
Dalapon	1,3-Dichloropropene
Diquat	Dicamba
Endothall	Iodomethane
Glyphosate	Chloropicrin
Oxamyl (Vydate)	Metribuzin
Simazine	Bentazon (Basagran)
Picloram	Molinate (Ordram)
Dinoseb	Thiobencarb (Bolero)
Aldicarb sulfoxide	Foaming agents
Aldicarb sulfone	Phenols
Metolachlor	1,2-Dibromo-3-chloropropane
Carbofuran	Ethylene dibromide
Aldicarb	Chlordane
Atrazine	<i>m</i> -Dichlorobenzene
Alachlor	Ethylbenzene
EPTC (Eptam)	Perchlorate
Butylate (Sutan)	Total aldicarbs
Cyanazine (Bladex)	Alpha-chlordane

Table 8.4 Sprawl and Urban Pollutants in U.S. Drinking Water

Ammonia	Dimethylphthalate
Arsenic	Diethylphthalate
Cadmium	Fluoranthene
Copper	Pyrene
Hydrogen sulfide	Di- <i>n</i> -butylphthalate
Lead	Butylbenzylphthalate
Mercury	Benzo[a]anthracene
Nitrate and nitrite mix	Benzo[b]fluoranthene
Nitrate	Benzo[k]fluoranthene
Nitrite	BaP
Phosphate	Indeno[1,2,3- <i>cd</i>]pyrene
Antimony	Dibenz[a,h]anthracene
Lithium	Benzo[g,h,i]perylene
Molybdenum	Alpha-lindane
Oil and grease total	Beta-lindane
Phosphorus	<i>Tert</i> -butylbenzene
Lindane	<i>Sec</i> -butylbenzene
Baygon (Propoxur)	Chloropicrin
Paraquat	Trichlorofluoroethane
Glyphosate	Phenols
Trifluralin	Xylenes (total)
Isopropyl alcohol	<i>p</i> -Xylene
Trichlorofluoromethane	<i>o</i> -Xylene
Acetone	<i>m</i> -Xylene
Naphthalene	Tetrachloroethylene
MTBE	Benzene
Fluorine	Bromobenzene
Phenanthrene	<i>n</i> -Propylbenzene
Anthracene	Ethyl- <i>tert</i> -butyl ether

It should be noted that not all water systems contained all the pollutants listed. The data are further broken down by state and local water supply systems on the Environmental Working Group website [65]. It should also be noted that many of the individual pollutants have more than one source. Heavy metals in potable water, e.g., may have their origin in mining, manufacturing, and/or power generation.

EPA has not established standards for all of the 260 chemicals. There are no MCL standards for 141 of the 260 chemicals found in U.S. drinking water. The unregulated water contaminants are listed in Table 8.8 [65].

As was seen in Section 8.8, under the Safe Drinking Water Act (United States Public Law 93-523, enacted in 1974), EPA is charged with setting MCLs for contaminants. To date, standards have been set for only 66 of these. Table 8.9 contains a list of the chemical contaminants for which EPA has established MCLs and their values [66]. All values are in milligrams per liter (mg/L). The chemicals are listed by category as disinfectants and DBPs, inorganic chemicals, organic chemicals, and radionuclides.

Table 8.5 Industrial Pollutants in U.S. Drinking Water

Aluminum	Arochlor 1221
Ammonia	Arochlor 1232
Bromide	Arochlor 1242
Arsenic	Arochlor 1248
Chlorate	Arochlor 1252
Barium	Arochlor 1260
Cadmium	1,1-Dichloropropene
Chromium	1,3-Dichloropropane
Cyanide	1,2,3-Trichloropropane
Hydrogen sulfide	2,2-Dichloropropane
Lead	1,2,4-Trimethylbenzene
Manganese	1,2,3-Trichlorobenzene
Mercury	<i>n</i> -Butylbenzene
Nitrate and nitrite (mix)	<i>Sec</i> -butylbenzene
Nitrate	<i>Tert</i> -butylbenzene
Nitrite	1,3,5-Trimethylbenzene
Phosphate	Bromochloromethane
Selenium	Chloropicrin
Silver	2-Nitropropane
Strontium	Glyoxal
Sulfate	Trichlorotrifluoroethane
Antimony	Foaming agents
Beryllium	Phenols
Chromium (hexavalent)	Ethylene dibromide
Lithium	Xylenes (total)
Molybdenum	<i>o</i> -Xylene
Thallium	<i>m</i> -Xylene
Vanadium	<i>p</i> -Xylene
MBAS (surfactants)	<i>m</i> - and <i>p</i> -Xylene (mix)
Oil and grease (total)	Formaldehyde
Phosphorus	Methylene chloride
Carbon disulfide	<i>o</i> -Chlorotoluene
Lindane	<i>p</i> -Chlorotoluene
<i>p</i> -Isopropyltoluene	<i>o</i> -Dichlorobenzene
Di(2-ethylhexyl)adipate	<i>m</i> -Dichlorobenzene
Di(2-ethylhexyl)phthalate	<i>p</i> -Dichlorobenzene
Hexachlorocyclopentadiene	VC
1,4-Dioxane	1,1-DCE
Endosulfan I	1,1-Dichloroethane
Butyl acetate	1,2-Dichloroethane
Ethyl ether	<i>Trans</i> -1,2-DCE
Isopropyl alcohol	1,1,1-Trichloroethane
Chloromethane	Carbon tetrachloride
Dichlorodifluoromethane	1,2-Dichloropropane
Bromomethane	TCE
Chloroethane	Tetrachloroethylene
Trichlorofluoromethane	1,1,2-Trichloroethane

(Continued)

Table 8.5 (Continued)

<i>n</i> -Nitrosodiphenylamine	1,1,1,2-Tetrachloroethane
Aniline	1,1,2,2-Tetrachloroethane
1,2-Dibromoethylene	Chlorobenzene
Acrylonitrile	Benzene
Acetone	Toluene
Isopropyl ether	Ethylbenzene
Hexachlorobutadiene	Bromobenzene
MEK	Isopropylbenzene
Naphthalene	Styrene
MIBK	<i>n</i> -Propylbenzene
MTBE	Perchlorate
Nitrobenzene	Ethyl- <i>tert</i> -butyl ether
Acenaphthylene	Dichlorofluoromethane
Acenaphthene	Alpha particle activity (including radon and uranium)
Dimethylphthalate	Alpha particle activity (excluding radon and uranium)
Diethylphthalate	Uranium (total)
Fluoranthene	Uranium-234
Pyrene	Uranium-235
Di- <i>n</i> -butylphthalate	Uranium-238
Butylbenzylphthalate	Radium (total)
Methyl methacrylate	Radium-226
Chrysene	Radium-228
Indeno[1,2,3- <i>cd</i>]pyrene	Alpha particle activity (suspended)
Dibenz[<i>a,h</i>]anthracene	Gross beta activity (dissolved)
PCP	Gross beta activity (suspended)
<i>n</i> -Hexane	Potassium-40
1,2,4-Trichlorobenzene	Tritium
<i>Cis</i> -1,2-DCE	Gross beta particles and photon emitters (man made)
Total PCBs	Manganese-54
Arochlor 1016	Strontium-90

In addition to the MCLs listed in Table 8.9, there are also secondary standards for water quality in the United States. The National Secondary Drinking Water Regulations (NSDWRs) are non-enforceable guidelines regulating contaminants that “may cause cosmetic effects (such as skin and tooth discoloration) or esthetic effects (such as taste, odor, or color) in drinking water” [66]. Many in the scientific community argue that the chemicals listed do not merely have cosmetic and esthetic effects, particularly when they are combined with other toxicants. EPA, however, recommends, but does not require, that water systems comply with these secondary standards. States, however, are permitted to adopt these as enforceable standards. The NSDWRs are listed in Table 8.10.

The MCL values for individual contaminants are based on amounts that would reasonably be expected to be consumed by humans in drinking water. This assumption fails to take into account absorption from non-ingestion sources. Chemicals

Table 8.6 Water Treatment and Distribution By-Product Pollutants in U.S. Drinking Water

Chloramine	Trichloroacetic acid (TCA)
Chlorate	Monobromoacetic acid
Chlorine dioxide	Dibromoacetic acid
Chlorite	Bromochloroacetic acid
Bromate	HAAs (total)
Cadmium	Dichloroacetonitrile
Orthophosphate	1,1-Dichloropropanone
Asbestos	Chloropicrin
Di(2-ethylhexyl)phthalate	Glyoxal
Chloromethane	Chloroform
MEK	Bromoform
2-Hexanone	Bromodichloromethane
Fluoranthene	Dibromochloromethane
Benzo[a]anthracene	TTHMs
Benzo[b]fluoranthene	Formaldehyde
Benzo[k]fluoranthene	<i>m</i> -Dichlorobenzene
BaP	Dichloriodomethane
Benzo[g,h,i]perylene	VC
Dibromomethane	Bromodichloroacetic acid
Bromochloromethane	Chlorodibromoacetic acid
Monochloroacetic acid	Tribromoacetic acid
Dichloroacetic acid	

Table 8.7 Naturally Occurring Pollutants in U.S. Drinking Water

Aluminum	Phosphorus
Ammonia	Chloromethane
Bromine	Alpha particle activity (excluding radon and uranium)
Arsenic	Alpha particle activity (including radon and uranium)
Chromium	Radon
Copper hydrogen sulfide	Total uranium
Lead	Uranium-234
Manganese	Uranium-235
Mercury	Uranium-238
Nitrate and nitrite mix	Total radium
Nitrate	Radium-226
Nitrite	Radium-228
Phosphate	Alpha particle activity (suspended)
Selenium	Gross beta particle activity (dissolved)
Silver	Gross beta particle activity (suspended)
Sulfate	Potassium-40
Hexavalent chromium	Gross beta particle and photon emitters (man made)
Lithium	

Table 8.8 Contaminants in U.S. Drinking Water for Which No MCLs Exist

Ammonia	Tetrahydrofuran
Bromide	Fluorine
Chlorate	2-Hexanone
Hydrogen sulfide	2,4-Dinitrotoluene
Phosphate	Phenanthrene
Orthophosphate	Anthracene
Strontium	Dimethylphthalate
Lithium	Diethylphthalate
Molybdenum	Fluoranthene
Vanadium	Pyrene
Oil and grease (total)	Di- <i>n</i> -butylphthalate
Phosphorus	Butylbenzylphthalate
Carbon disulfide	Methyl methacrylate
Deisopropylatrazine	Chrysene
Carbaryl	Benzo[a]anthracene
Methomyl	Benzo[b]fluoranthene
Baygon (Propoxur)	Benzo[k]fluoranthene
Methiocarb	Indino[1,2,3- <i>cd</i>]pyrene
Acetochlor	Dibenz[ah]anthracene
Paraquat	Benzo[g,h,i]perylene
Prometon	Aldrin
<i>p</i> -Isopropyltoluene	<i>n</i> -Hexane
Aldicarb	Dibromomethane
Aldicarb sulfoxide	1,1-Dichloropropene
Aldicarb sulfone	1,3-Dichloropropane
Metolachlor	1,2,3-Trichloropropane
1,4-Dioxane	<i>n</i> -Butylbenzene
Eptam	1,3,5-Trimethylbenzene
Sutan	<i>Tert</i> -butylbenzene
Cyanazine	<i>Sec</i> -butylbenzene
Trifluralin	Bromochloromethane
Ethion	Dicamba
3-Hydroxycarbofuran	Bromochloroacetic acid
Endosulfan I	Iodomethane
Dieldrin	Dichloroacetonitrile
DDT	1,1-Dichloropropanone
Butachlor	Chloropicrin
Propachlor	2-Nitropropane
Butyl acetate	Glyoxal
Ethyl ether	Metribuzin
Isopropyl alcohol	Bentazon
Bromacil	Molinate
Dacthal	Thiobencarb
Diuron	Trichlorotrifluoroethane
2,4-DB	Phenols

(Continued)

Table 8.8 (Continued)

2,4,5-T	Formaldehyde
Chloramben	<i>o</i> -Chlorotoluene
Dichlorprop	<i>p</i> -Chlorotoluene
Chloromethane	<i>m</i> -Dichlorobenzene
Bromomethane	Dichloriodomethane
Dichlorodifluoromethane	1,1-Dichloroethane
Chloroethane	1,1,1,2-Tetrachloroethane
Trichlorofluoromethane	1,1,2,2-Tetrachloroethane
<i>n</i> -Nitrosodiphenylamine	Bromobenzene
Aniline	Isopropylbenzene
1,2-Dibromoethylene	<i>n</i> -Propylbenzene
Acrylonitrile	Potassium-40
Acetone	Tritium
Isopropyl ether	Manganese-54
Hexachlorobutadiene	Strontium-90
MEK	Perchlorate
Naphthalene	Total aldicarbs
MIBK	Bromodichloroacetic acid
MTBE	Chlorodibromoacetic acid
Nitrobenzene	Tribromoacetic acid
Acenaphthylene	Alpha-chlordane
Acenaphthene	Ethyl- <i>tert</i> -butyl ether
Isophorone	Dichlorofluoromethane

can be absorbed from dermal and eye contact with aqueous solutions containing toxicants [67, 68]. Volatile organic compounds dissolved in water can be released upon heating as is the case in cooking and warming of wash water. Such volatilized organic compounds can be absorbed by inhalation and dermal contact. Benzene provides an example of this phenomenon. Benzene is readily absorbed via inhalation, but is also taken up through the skin when cleaners containing it as an impurity are used. Such combined uptake has been calculated to increase the risk for leukemia [20]. The risk for spontaneous abortion from exposure to THMs in household water supplies is similarly increased by a combination of ingestion, inhalation, and dermal absorption [20].

8.11 Mixtures

It is quite obvious that with all the different toxic chemicals found in drinking water, an almost infinite number of mixtures can be envisioned. As was pointed out above in the example of DBPs, it is close to impossible to predict what the true cause of a health effect derived from exposure to contaminated water is (Section 8.9). There are few studies that definitively demonstrate such a connection. One, however, does

Table 8.9 EPA MCLs for Drinking Water

Disinfectants and DBPs	
Contaminant	MCL (mg/L)
Chloramines	4.0
Chlorine	4.0
Chlorine dioxide	0.8
Bromate	0.010
Chlorite	1.0
HAAs	0.060
TTHMs	0.080
Inorganic Chemicals	
Antimony	0.006
Arsenic	0.010
Asbestos	7 million (fibers per liter)
Barium	2
Beryllium	0.004
Cadmium	0.005
Chromium (total)	0.1
Copper	1.3
Cyanide	0.2
Fluoride	4.0
Lead	0.015
Mercury	0.002
Nitrate	10
Selenium	0.05
Thallium	0.002
Organic Chemicals	
Acrylamide	Restricted use by formula
Alachlor	0.002
Atrazine	0.003
Benzene	0.005
BaP (PAHs)	0.0002
Carbofuran	0.04
Carbon tetrachloride	0.005
1,2-Dichloropropane	0.005
Di(2-ethylhexyl)adipate	0.4
Di(2-ethylhexyl)phthalate	0.006
Dinoseb	0.007
Dioxin (2,3,7,8-TCDD)	0.0000003
Diquat	0.02
Endothall	0.1
Endrin	0.0002
Epichlorohydrin	Restricted use by formula
Ethylbenzene	0.7

(Continued)

Table 8.9 (Continued)

Disinfectants and DBPs	
Contaminant	MCL (mg/L)
Glyphosate	0.7
Heptachlor	0.0004
Heptachlor epoxide	0.0002
Hexachlorobenzene	0.001
Hexachlorocyclopentadiene	0.05
Lindane	0.0002
Methoxychlor	0.04
Oxamyl (Vydate)	0.2
PCBs	0.0005
PCP	0.001
Picloram	0.5
Simazine	0.004
Styrene	0.1
Tetrachloroethylene	0.005
Toluene	1
Toxaphene	0.003
2,4,5-TP (Silvex)	0.05
1,2,4-Trichlorobenzene	0.07
1,1,1-Trichloroethane	0.2
1,1,2-Trichloroethane	0.005
TCE	0.005
VC	0.002
Xylenes (total)	10
Radionuclides	
Alpha particles	15 pCi/L
Beta particles and photon emitters	4 mrem/year
Radium-226 and -228 combined	5 pCi/L
Uranium	30 µg/L

just that. It was reported by Porter et al. that although there was little or no observed biological effect on mice of nitrates alone, aldicarb alone, or atrazine alone when they were consumed at the MCLs for groundwater, the combination of pesticide and nitrate altered immune, endocrine, and nervous system parameters [16]. Though human exposure was not addressed in that study, it is significant because it demonstrated how wide-ranging the unexpected effects of exposure to even minute quantities of chemical mixtures of lipophiles and hydrophiles can be. This study serves as a warning on the dangers of drinking water contaminated with mixtures of chemicals.

Table 8.10 NSDWRs for Potable Water in the United States

Contaminant	Secondary Standard
Aluminum	0.05–0.2 mg/L
Chloride	250 mg/L
Color	15 (color units)
Copper	1.0 mg/L
Corrosivity	Noncorrosive
Fluoride	2.0 mg/L
Foaming agents	0.5 mg/L
Iron	0.3 mg/L
Manganese	0.05 mg/L
Odor	3 threshold odor number
pH	6.5–8.5
Silver	0.10 mg/L
Sulfate	250 mg/L
Total dissolved solids	500 mg/L
Zinc	5 mg/L

8.12 Toxic Landfill Runoff

Landfills are areas heavily contaminated with mixtures of toxic chemicals which regularly leach and contaminate surface waters and groundwaters. Though industrial landfills are generally more heavily contaminated, municipal landfills also carry sizable toxic loads and both varieties leach mixtures of lipophiles and hydrophiles that include organic, inorganic, and heavy metal toxicants to groundwater and surface water [69–72]. The leaching process often involves chemical reactions that result in heavy metals being bound by dissolved organic molecules in metal–organic complexes that precede migration into drinking water sources [70, 73].

Drinking water taken from surface water and groundwater sources close to landfills has been shown to result in increased incidences of birth defects and cancers. Congenital heart disease, neural tube, heart, oral cleft, central nervous system, and musculoskeletal defects have been reported in children born to mothers who drank water contaminated with toxic chemicals from landfill runoff sites [71, 72, 74–76]. Non-Hodgkin's lymphoma, gastrointestinal, bladder, pancreatic, liver, and kidney cancer incidences are significantly elevated for those drinking water polluted by toxic landfill runoff [77–80]. In none of the cancer clusters that have been studied has any association between increased cancer incidences and exposures to single chemicals been made. All exposures, however, were to mixtures of lipophiles and hydrophiles [81]. Cancer clusters will be discussed in Chapter 33.

8.13 Summary

Water pollution causes the introduction of a very wide variety of toxic chemicals to those drinking, cooking, and bathing with impure water. There are numerous sources of pollutants that end up in potable water and the mixtures produced by many of these pollutants result in unexpected toxic effects in people who consume such water. Mixtures of lipophilic and hydrophilic chemicals have been demonstrated to be causative for many of these unanticipated toxic effects.

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9 Soil Pollution

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9.1 Introduction

Soil is defined as follows: “(i) The unconsolidated mineral or organic material on the immediate surface of the earth that serves as a natural medium for the growth of land plants. (ii) The unconsolidated mineral or organic matter on the surface of the earth that has been subjected to and shows the effects of genetic and environmental factors of climate (including water and temperature effects) and macro- and micro-organisms, conditioned by relief, acting on parent material (material in which soils form) over a period of time. A product-soil differs from the material from which it is derived in many physical, chemical, biological, and morphological properties and characteristics” [1].

This broad definition accommodates numerous variations in soil composition. The National Cooperative Soil Survey identifies more than 20,000 different kinds of soil in the United States alone [2]. Soil formation is a dynamic, ongoing process dependent upon climate (wind, water availability, temperature), topography, time, and biological activity of plants, animals, and micro-organisms.

The chemical composition of soil is complex, naturally containing numerous inorganic and organic compounds. Pollution of soil may be accomplished via the addition of chemical species that are alien to soil, such as organochlorine pesticides, or through the addition of quantities of naturally occurring chemicals which at elevated concentrations are toxic. Examples of the latter are chloride and heavy metals such as copper and selenium.

The toxicological impact of polluted soil on humans is indirect. Chemical pollutants in soil affect the ability of soil to support plant life (fertility) by depressing

micro-organistic and soil-dwelling animal activities. Plants growing in polluted soil absorb toxic chemicals through their root systems and induce toxic effects in humans when those plants are ingested. Polluted soil also adversely affects humans via bioaccumulation of toxic chemicals in animals when plants that have absorbed these chemicals from polluted soil are eaten or when they are dermally absorbed by animals that come in contact with such soil.

9.2 Depressed Microbial Activity

Healthy bacterial populations are essential for soil fertility. Heavy metals, pesticides, and petroleum chemicals are toxic to soil micro-organisms. Illustrative examples of the impacts of these toxins are as follows.

Elevated copper and zinc concentrations in soil adversely affect microbial biomass, activity, and composition of microbial communities in soil adjacent to copper smelters and copper-tailing dumps [3, 4]. Nitrogen fixation was adversely impacted when heavy-metal-contaminated sewage sludge was added to soils [5].

The herbicide Paraquat was found to cause mutations in nitrogen-fixing soil bacteria and reduce chlorophyll content of algae [6, 7]. DDT and its metabolites DDE and DDD (dichlorodiphenyldichloroethane) are widespread soil pollutants that alter the species composition of soil algae and nitrogen-fixing bacteria and entirely eliminate some species of these [8]. The pesticides hexaconazole, carbofuran, and ethion are toxic to soil microflora and result in the reduction of soil bacteria counts [9].

Petroleum hydrocarbons are widespread soil pollutants. The sources of this pollution are gasoline and fuel oil transport spills, surface and underground storage tank leaks, refinery spills, refinery and creosote manufacturing sludges, petrochemical plant effluents, and many others. Petroleum hydrocarbons present in soil are cytotoxic and result in reductions of microbial biomass, soil enzyme activity, and microalgae populations [10, 11]. These hydrocarbons are also mutagenic to soil micro-organisms [12].

9.3 Toxicity to Soil-Dwelling Animals

Soil-dwelling animals increase soil fertility by aerating the soil and decomposing organic matter. Pollutants in soil are toxic to these animals. Rodents (mammals) that live in soil are exposed to soil toxins via ingestion of insects, earthworms, and plant roots as well as via dermal contact. In one study, soil contaminated with PAHs was shown to be toxic to the duodenum, lungs, kidneys, spleen, and liver of test animals [13].

Insects and earthworms have a more intimate contact with soil pollutants and generally serve a more useful function in soil fertility. Earthworms have proven to be an easy species to study with regard to soil-polluting effects. Lead, cadmium, and copper are readily absorbed by earthworms. In high concentrations, these heavy metals

are lethal. In lower concentrations, they accumulate in the earthworm, causing toxic effects that are manifested in reduced activity by the earthworms [14, 15].

Pesticides in soils are acutely toxic and genotoxic to earthworms. The pesticides imidacloprid and RH-5849, for example, have been shown to be lethal at high concentrations and to induce significant DNA damage at lower concentrations [16].

9.4 Plant Absorption of Soil Toxins and Bioaccumulation

Soil contaminated with toxic chemicals is toxic to plants as well as to animals. The effects of heavy metals on plant growth have been extensively studied. The following are examples of this phenomenon.

Copper exhibits rhizotoxicity in wheat seedlings [17]. Copper and chromium retard shoot and root growth of barley [18]. The yield of wheat is decreased when soil is contaminated with cadmium oxide or zinc oxide [19]. Copper and nickel smelter-polluted soil retards biomass growth of pine trees and reduces the essential calcium, potassium, and magnesium contents of saplings [20]. Cadmium in the soil reduces ryegrass growth with crop yields inversely proportional to cadmium content [21].

Plants that grow in contaminated soils can absorb those pollutants. Once absorbed, such toxic chemicals are taken up by animals that feed on the contaminated plants and passed up the food chain, in many instances, to humans. The following are examples of such an effect.

Prairie grass absorbs pesticides present in the soil in which it grows. Atrazine, alachlor, metolachlor, and pendimethalin are examples of these [22]. Cattle grazing on grass so contaminated bioaccumulate pesticides and pass these along to humans who eat the cattle. PCBs, polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans are transferred to biota that grow in contaminated soils. Foraging animals (chickens and ducks) that eat biota thus contaminated have been shown to be highly contaminated with those toxins [23]. People eating such chickens or ducks are thus exposed to high levels of extremely toxic chemicals. Other lipophilic chemicals, such as petroleum hydrocarbons (aromatic hydrocarbons and PAHs), are also readily absorbed from soil and passed up the food chain to humans [24].

Heavy metals absorbed by crops from contaminated soils are also passed up the food chain. Cadmium, zinc, and lead are absorbed by wheat and rice plants [19]. Cultivated ryegrass absorbs cadmium from polluted soil [21]. Ryegrass is a crop fed to cattle, which absorb the cadmium and pass it up the food chain to humans.

9.5 Effects of Mixtures

Some of the effects of toxic chemical mixtures on soil pollution are predictable. Acidic soils dissolve otherwise insoluble metal oxides and salts, thereby increasing available metal concentrations and toxicity to flora and fauna. Available copper content is

inversely proportional to increased pH of soil [4]. Earthworm mortality in soil polluted by lead increases as pH decreases [15]. The addition of ethylenediaminetetra-acetic acid (EDTA) and its disodium salt to soil contaminated with cadmium, lead, and zinc increases the availability of these metals to plants and results in significant increases of uptake of these in plants [25].

Other effects of toxic chemical mixtures on soil are not predictable. Mixtures of fertilizers and pesticides produce enhanced toxic effects. The additions of urea, superphosphate, and potash enhance the toxicities of carbaryl and carbofuran insecticides to nitrogen-fixing bacteria in soil [26]. Soil co-contaminated with arsenic and DDT does not break down DDT as rapidly as soil contaminated with DDT alone. This results in a persistence of DDT in the environment [27].

Chlorinated hydrocarbons are persistent VOC pollutants that infiltrate soil from disposal of dry-cleaning fluids, degreasing solvents, food extraction solvents, and paint strippers. TCE is illustrative of these compounds.

TCE, a widely used solvent and degreaser, is believed to be a carcinogen and mutagen. It is a dense nonaqueous-phase liquid (DNAPL) which displaces water, sinks into the soil subsurface, and permeates through the soil into groundwater. Some of the TCE, however, is bonded to lipophilic soil molecules which help retain it in the soil. TCE also accumulates in soil voids where it persists for long periods of time [28]. Bacteria slowly biotransform TCE to the dichloroethanes, dichloroethylenes, and VC (similar to the transformation described for TCE in groundwater in Section 8.9) but this process is slow, resulting in the persistence of TCE in soil for years [29]. TCE in soil acts as a solvent for other organic molecules and pesticides and contributes to the retention of these toxic compounds in soil for long periods of time and forms toxic mixtures with unknown consequences.

Contaminated sites such as industrial chemical dumps contain mixtures of numerous toxicants. These include multiple lipophiles and hydrophiles that can undergo chemical reactions, migrate, and be absorbed by plants and animals [30]. Such sites are often acutely and chronically toxic, environmentally persistent, and lead to bioaccumulation of toxicants in food webs. An excellent example of such a site is Love Canal in New York State.

From 1942 to 1952, Love Canal was used as a disposal site for over 21,000 tons of chemical wastes, including halogenated organics, pesticides, chlorobenzenes, and dioxins. In 1953, the landfill was covered and deeded to the Niagara Falls Board of Education. Subsequently, the area near the landfill was extensively developed with an elementary school and numerous houses were constructed. In the 1960s and 1970s, groundwater levels under the landfill rose, and more than 100 lipophilic and hydrophilic organic compounds leached out, contaminating the air and drinking water supplies of thousands of people. The health effects of exposure to these chemicals include high rates of birth defects, immune system suppression, various cancers, and chromosome damage. Children exposed were diagnosed with elevated numbers of seizures, learning problems, hyperactivity, skin rashes, eye irritation, abdominal pain, and incontinence [31]. Though some of these effects could be attributed to individual compounds (the immunosuppression effects of TCDD [32]),

most of the problems reported could not be ascribed to the individual chemicals found. It is hypothesized that the unexpected effects were caused by exposures to mixtures of lipophilic and hydrophilic chemicals [33].

9.6 Summary

Soil contamination can contribute to human toxic exposure via a number of routes. These include plant uptakes of soil pollutants, including fertilizers and pesticides, that are either eaten by people directly or passed up the food chain, absorption onto the skin and subsequently into the bodies of grazing animals to be passed up through the food chain by animals, and via contaminated airborne soil particles that are ultimately inhaled by humans. Soils contain large lipophilic components that absorb lipophilic chemicals which are subsequently transferred to plants, animals, and to the air. Water distributed in soil dissolves hydrophilic chemicals and acts as a conduit for ultimate human absorption via plant uptake and progression up the food chain.

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10 Food

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10.1 Introduction

Food, along with air and water, is essential for survival. Much of human culture is centered around food preparation and consumption. In the twentieth century, food production and preparation in many parts of the world moved from small farms, home and restaurant kitchens, and small food preparation businesses (e.g., local bakeries) to giant food growing and processing operations. Along with these changes, many chemicals were introduced into food.

Though not foods, the “inactive” ingredients in pharmaceutical products, vitamins, and mineral supplements contain many of the same chemicals added to commercially produced foods. These are considered in this chapter as well.

Xenobiotics present in food arise from one of the following five sources:

1. Uptake by fruits and vegetables from soil and plant surfaces while growing.
2. Ingestion of treated food and water by cattle, fowl, and fish.
3. Food preparation.
4. Additives in commercial food preparations.
5. Packaging.

Though the presence of some xenobiotics in food is inevitable, given their presence in air, water, and soil, others are deliberately added for esthetic, preservation, and economic purposes.

Fertilizers containing nitrates, phosphates, and heavy metals are applied to soil to increase yields of crops. Insecticides, herbicides, and fungicides are applied to food crops to reduce losses to “pest” species. As was discussed in Chapter 9, these chemicals may be absorbed into the roots of plants and passed up the food chain to humans by animals that consume such plants. These chemicals may also be directly consumed by humans who eat the treated plants.

Plants consumed by humans are further contaminated with toxic chemicals arising from agricultural runoff, industrial runoff, urban runoff, and environmental spread of persistent organic pollutants (POPs) into growing fields.

Animals that are hunted and fished for as food often contain bioaccumulated residues of toxic chemicals. These include mercury, PCBs, dioxins, and organochlorine compounds (including pesticides).

Animals raised for their meat are deliberately fed hormones to induce rapid growth and antibiotics to keep them healthy. These are transferred to humans when their meat is eaten. Farm and ranch animals are often sprayed with pesticides that are absorbed through their skins and ultimately consumed by humans.

It is beyond the scope of this book to examine all the sources of toxic chemical contamination of foods consumed by humans. The sections that follow address the absorption of xenobiotic chemicals via plant and animal growth and by the addition of toxic chemicals to food and pharmaceuticals during their preparation and packaging.

10.2 Persistent Organic Pollutants

POPs are pervasive in our environment. They are present virtually everywhere in the world, including the arctic environs [1]. Food is the primary source of human exposure to POPs. As was discussed in Chapter 9, they are taken up by plants grown in contaminated soil [2]. For example, alpha-endosulfan, beta-endosulfan, and endosulfan sulfate were absorbed by lettuce growing in soil contaminated with these pesticides [3].

POPs are found in the flesh of animals in all the world's environments. The examples that follow are illustrative.

Fish eaten by people residing in northern Norway are contaminated with PCBs, chlorinated pesticides, and their metabolites [4]. Fish living in mangrove habitats in Singapore are contaminated with PBDEs [5]. Dioxins and PCBs are found in the eggs of free-range chickens [6].

POPs are widespread in human food products [7]. An indication of the pervasiveness of POPs is seen from a worldwide study of butter contamination with PCBs, polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), HCB, and DDT and its metabolites. These POPs were found to be present in varying degrees in the butter of 37 different nations [8].

PCDDs, PCDFs, PCBs, PBDEs, and organochlorine pesticides are contaminants of human breast milk [9, 10]. PCBs and PBDEs are found in human adipose and muscle tissues [11].

10.3 Mercury

Mercury in its elemental form is a liquid that is vaporized upon heating. It is a component of fossil fuel and is found in airborne emissions from fossil-fuel burning plants. It travels through the environment via several pathways, including air, water, and bioaccumulation routes [12].

Inorganic mercury released into the environment is converted by micro-organismic activity into MeHg, a persistent pollutant that is soluble in adipose tissue and passed up the food chain. As a result, predator fish species are significantly more contaminated with MeHg than those that feed on plants and benthic organisms. For example, it has been found that in Canada's Arctic and Subarctic regions, benthic feeding fish such as whitefish have significantly lower MeHg in their flesh than trout, pike, and walleye, which are predatory [12].

MeHg is toxic to humans, causing central and peripheral nervous system injuries [13]. Those who are exposed suffer a degeneration of their nervous systems. Symptoms include numbness in lips and limbs, involuntary movement, constricted vision, slurred speech, and hallucinations. The most famous historic example of MeHg poisoning is the Minamata Disease outbreak in Japan [14].

In the 1950s a petrochemical plant dumped an estimated 27 tons of mercury waste into Minamata Bay. A short while after the dumping began, people started noticing that cats in the adjacent town appeared to be going insane and were falling into the sea. Soon thereafter, people in the town became symptomatic as described earlier. Children of poisoned mothers were born with severe deformities, mental retardation, blindness, and deafness. Investigation revealed that the animals and humans of Minamata, who consumed large quantities of locally caught fish, were poisoned by MeHg, which had been formed in situ in the bay and passed up the food chain from fish to people. In total, almost 3000 people contracted Minamata Disease [14].

Organic mercury pollution is not limited to salt water environments. This pollution is extensive in lakes and rivers as well. People who consume fish contaminated with MeHg, even at low levels, have reduced neurobehavioral performance [15]. In the United States, many state agencies recommend limiting the eating of fish taken from these waters, particularly for pregnant women.

Organic mercury is also consumed by people in the form of preservatives used in pharmaceuticals. The controversy surrounding this use will be discussed in Chapter 20.

10.4 Antibiotics in Meat

Antibiotics are used by meat producers to improve animal production and treat diseases. These are administered to beef and dairy cattle, swine, broiler chicks, and laying hens [16]. Prophylactic antibiotics are also widely administered in fin-fish aquaculture to prevent bacterial infections that result from poor sanitation in fish farming [17].

The administering of antibiotics to animals and fish leads to the accumulation of residues in the animals' flesh and subsequent ingestion by humans. Such antibiotic residues are due to the development of cytotoxic effects and reduced capacities of detoxification and excretion organs in the treated animals [16]. In the United States, the federal government has established antibiotic residue tolerances and specifies target tissues for residue monitoring. When muscle tissue is specified as the target tissue for testing, the federal standards do not specify which muscle tissue is to be examined. In poultry, for example, breast muscle accumulates antibiotic residues at higher concentrations than thigh muscle does [16].

The effects on humans following consumption of meats with antibiotic residues have not been well-studied. It is surmised that such residues help lead to antibiotic-resistant bacteria with obvious human end points.

10.5 Steroids in Meat

Anabolic agents are used to increase the rate of growth in livestock [18, 19]. Both steroids that are naturally present in the body (endogenous steroids) and those that

are foreign to the body (exogenous steroids) are used for this purpose. Exogenous steroids include esters of endogenous steroids (e.g., estradiol benzoate and testosterone propionate) or compounds with modified steroidal structures such as trenbolone acetate [18]. All these compounds, however, have one characteristic in common: they are transferred through the food chain to humans who consume the treated animals.

Steroids in meat consumed by humans have the propensity to produce endocrine disrupting effects. Estradiol, progesterone, and testosterone, which are fed to meat animals, occur naturally in both humans and animals in identical molecular forms. Consuming meat with these compounds in them raises the levels of these hormones in the human body. Very little is known about the effects of such increases in hormone levels in humans. Even less is known of the effects on children [20].

The effects of exogenous steroids can differ from those of endogenous steroids in several ways. Firstly, the biological activity of exogenous sex hormones can be much stronger. Secondly, they may be metabolized differently, and thirdly, they may induce effects that are different from those of endogenous steroids [20].

The effects on humans of eating meat contaminated with steroids are in the early stages of study. One of the effects suspected is the early onset of puberty in children who consume large quantities of steroids. This will be explored in more detail in Chapter 23.

10.6 Additives in Commercial Food Preparation

Food additives are chemical substances, other than basic foods, used in commercial food preparation to achieve preservative, flavor, color, stability, and esthetic effects. Though some of the chemicals used are derived naturally, most of the additives used in food production are synthetic and with little or no nutritional value [21, 22]. A glance at almost any cookbook shows that chemical additives are not necessary for food preparation. Their use allows inferior ingredients to be used, extends the shelf lives of many products, and exposes people to toxic chemicals.

The basic reasons for using food additives are:

1. *Emulsification*: Emulsifiers, such as lecithin, are used to keep oil and aqueous phases in salad dressings from separating.
2. *Thickening*: Thickeners, such as carrageenan and carboxymethyl cellulose, are used to thicken ice cream and jelly and impart texture to bread and cake.
3. *Enrichment*: Vitamins and minerals, such as vitamin D, thiamin, and niacin, are added to fortify milk and flour.
4. *Anticaking*: Anticaking agents, e.g., sodium aluminosilicate in salt, silicon dioxide in powdered milk, and nondairy creamers, are used to prevent coagulation.
5. *Chelation*: Chelating agents, such as EDTA, are added to prevent precipitation of insoluble metal salts. Citric acid and tartaric acid are other chelating agents that are added to prevent discoloration during food processing.
6. *Bleaching*: Bleaching agents, such as peroxides, are used to whiten flour and cheese.
7. *Preservation*: Antimicrobial agents, such as methyl paraben, propyl paraben, sodium benzoate, and calcium propionate, are added to many foods to prevent food spoilage caused

by mold, bacteria, fungi, or yeast. The use of preservation chemicals extends the shelf lives of many foods and eliminates the need for refrigeration of others.

8. *Antioxidant activity*: Antioxidants, such as butylated hydroxyanisole (BHA) and BHT, prevent fats and oils from reacting with oxygen and becoming rancid.
9. *Coloring*: Artificial colors, such as blue #1, yellow #6, and red #40, are added to impart appealing colors virtually to every type of prepared food.
10. *Flavoring*: Artificial flavors, such as saccharin for sugar and benzaldehyde for cherry flavor, are used as substitutes for natural flavors. Flavor enhancers, such as monosodium glutamate (MSG), have little or no flavor of their own but are used to enhance the flavor of other food compounds.

10.7 Chemical Impurities in Food: Allowable Xenobiotics

In the United States, the Federal Food, Drug and Cosmetic Act of 1938 (FD&C) gave FDA the authority to oversee and regulate food and food ingredients. The Food Additives Amendment to the FD&C of 1958 requires FDA approval for food additives usage prior to their incorporation into food and also requires the manufacturer to prove an additive's safety for the way it will be used. There are, however, exceptions to the regulation. All additives that were determined by the FDA or the USDA to be safe for use in specific foods prior to the 1958 amendment were designated as prior-sanctioned substances (an example being nitrites used in luncheon meats). Food additives that had either a history of use in food prior to the 1958 amendment or published scientific evidence of their safe use in food were also excluded from the requirement that manufacturers prove their safety. Such food ingredients are designated as "generally regarded as safe" (GRAS) [23]. The GRAS list contains hundreds of chemical additives, including MSG, calcium propionate, BHA, and BHT. It does not contain those chemicals determined by the manufacturers to be covered under the GRAS classification and not requiring notification nor label listing.

The list of chemical additives in foods is not limited to those on the GRAS list. More than 3000 chemicals are permitted to be present in food in the United States. These are listed in an FDA database referred to as Everything Added to Food in the United States (EAFUS) [24]. This list includes chemicals used in food processing, chemicals arising from machinery used in food processing, extraction solvent residues, pesticide residues, antibiotics, growth hormones, and chemicals deliberately added to food. Though the list is long, it does not contain all food additives. Some of these are chemicals added under a GRAS determination made independently of FDA. A partial list of volatile organic EAFUS listed additives and the known target organs for each compound is given in Table 10.1. Entries with C after their names are known or suspected carcinogens. Those with T after their names are teratogenic.

The list in Table 10.1 contains numerous lipophiles and hydrophiles. A vast number of mixture combinations are possible. Though most mixtures have not been studied, one possible binary mixture from this list, hexane and MEK, has a known synergism. MEK (as well as other ketones on the EAFUS list not shown in Table 10.1) potentiates the neurotoxicity of hexane [26].

Table 10.1 Partial List of EAFUS Database. All Chemicals Listed Target the Skin and Eyes

Chemical	Target Organs
Acetaldehyde	RES, CNS
Acetophenone	CNS
Acrolein C, T	Heart, RES
Amyl alcohol	RES, CNS
Anisole	RES
Benzene C	RES, CNS, blood, bone marrow
Chloroform	CNS, LIV, KID, heart
Cyclohexane	CNS
Diethyl amine	RES, LIV, KID
Ethyl acetate	RES, CNS, RPS
Ethyl acrylate C, T	RES, LIV, KID
Ethylene oxide C	RES, KID, adrenal glands, skeletal muscles, RPS
Glutaraldehyde	RES, CNS, LIV
Hexane	RES, CNS, PNS
Hydrazine C	RES, CNS, KID
Hydrogen sulfide	RES, CNS
Methanol T	RES, CNS, GI
MEK	RES, CNS
Methyl methacrylate T	RES, CNS, PNS, KID, LIV
Methylene chloride C	RES, CNS, LIV, blood
Monoethanolamine	RES, CNS, KID, LIV, blood
Phenol	RES, CNS, LIV, KID, heart
Propylene glycol	RES
Pyridine	RES, CNS, LIV, KID
Styrene C	RES, CNS
TCE C	RES, CNS, PNS, KID, LIV
Vinyl acetate T	RES, CNS, heart

Source: Toxicology data after Sittig [25].

RES, respiratory system; CNS, central nervous system; PNS, peripheral nervous system; GI, gastrointestinal system; KID, kidneys; LIV, liver; RPS, reproductive system. Carcinogens are denoted by C after the name, teratogens by T after the name.

It is not implied here that all the toxic chemicals listed on the EAFUS list are present in all foods, or in any one meal. Many food additives, however, contain large numbers of toxic chemicals.

Food additives number in thousands. Addressing all of these is beyond the scope of this book. The following sections are illustrative of the toxicants used in commercial food preparation.

10.8 Flavor Additives

Flavor additives are widely used. As an example, let us consider the composition of an artificial strawberry flavoring used in strawberry milk shakes as shown in Table 10.2 [27].

Table 10.2 Chemical Ingredients in an Artificial Strawberry Flavor Used for Thick Shakes

Amy acetate	Hydroxyphenyl-2-butanone
Amyl butyrate	α -Ionone
Amyl valerate	Isobutyl butyrate
Anisyl formate	Lemon essential oil
Benzyl acetate	Maltol
Benzyl isobutyrate	Menthol
Butyric acid	4-Methylacetophenone
Cinnamyl valerate	Methyl anthralnilate
Cognac essential oil	Methyl benzoate
Diacetyl	Methyl cinnamate
Dipropyl ketone	Methyl heptine carbonate
Ethanol	Methyl naphthyl ketone
Ethyl acetate	Methyl salicylate
Ethyl amyl ketone	Mint essential oil
Ethyl butyrate	Nerolin
Ethyl cinnamate	Neryl isobutyrate
Ethyl heptanoate	Orris butter
Ethyl heptylate	Phenethyl alcohol
Ethyl lactate	Rose
Ethyl methyl phenylglycidate	Rum ether
Ethyl nitrate	γ -Undecalactone
Ethyl propionate	Vanillin
Ethyl valerate	Solvent (unspecified)
Heliotropin	

Here, again, numerous mixtures are possible. An example of a toxic binary mixture of chemicals on this list shows a synergistic effect. When administered together, ethanol inhibits the metabolism of ethyl acetate, resulting in greater toxicity of ethyl acetate [28].

Synthetic raspberry flavoring is comprised of the following chemicals:

Vanillin
 Ethylvanillin
 Alpha-ionone
 Maltol
 1-(*p*-Hydroxyphenyl)-3-butanone
 Dimethyl sulfide
 2,5-Dimethyl-*N*-(2-pyrazinyl)pyrrole [27].

The vanillin in the mixture is not a natural product. Natural vanilla extract is a mixture of hundreds of compounds in addition to vanillin. Artificial vanilla flavoring is a solution of pure synthesized vanillin, 4-hydroxy-3-methoxybenzaldehyde. Mixtures of vanillin with other toxicants enhance mutagenic effects [29] and produce synergistic inhibition of lignocellulose degradation when mixed with catechol [30].

Vanillin potentiates the hepatotoxicity of carbon tetrachloride [31]. Mixtures of vanillin and cigarette smoke condensates induce sister-chromatid exchanges [32].

10.9 Artificial Food Colors

Artificial food colors are synthetic dyes manufactured from petroleum that have no nutritional value. Some of these are, however, neurotoxic and others contain carcinogenic components [33–35]. For example, some children whose diets contained artificial food colors were found to exhibit symptoms of ADHD. This effect is discussed in Chapter 21. Removal of the artificial food colors from their diets eliminated the symptoms [33]. In vitro exposures to a mixture of blue #1 and yellow #5 were found to induce malignant cell transformation [36].

10.10 Flavor Enhancers: MSG

MSG is commercially (and even at home) added to many foods as a flavor enhancer despite the fact that it is an excitatory neurotoxin that can freely penetrate certain brain regions and rapidly destroy neurons by hyperactivating *N*-methyl-D-aspartate (NMDA) receptors, a property of MSG that makes the nervous systems of the developing fetus particularly vulnerable to this excitotoxin [37].

Symptoms reportedly developed following ingestion of MSG include tingling, a burning sensation or a radiating numbness in the back of the neck, forearms, and chest; facial pressure tightness; chest pain; headache; nausea; rapid heartbeat; mouth and throat dryness; drowsiness; and weakness [21, 38, 39].

In a blind study, MSG ingestion has been demonstrated to induce asthma in people who have this condition. Forty-one percent of those tested developed asthma and other symptoms of MSG ingestion within 1–2 h of eating MSG-containing food [40].

MSG has also been associated with fibromyalgia syndrome (FM). FM is a painful rheumatologic disorder that is difficult to treat. Patients diagnosed with FM for 2–17 years had complete or almost complete elimination of their symptoms within months of removing MSG or MSG plus aspartame from their diets. All patients have had recurrence of their symptoms whenever they ingested MSG [41].

10.11 Aspartame: Non-Nutritive Sweetener

Aspartame is a non-nutritive sweetener that was first allowed by the FDA for use in dry foods in 1981 and approved for beverages in 1983. Aspartame is consumed by tens of millions of people as it is present in beverages, instant breakfasts, desserts, breath mints, sugar-free chewing gum, vitamins, pharmaceuticals, and numerous other products. Though it offers diabetics, dieters and others who must limit sugar

intake an alternative sweetening choice, it is toxic. Those consuming it have complained of neurologic, gastrointestinal, and allergic reactions [42].

Aspartame is completely metabolized in the gut and absorbed as aspartic acid, phenylalanine, methanol, and diketopiperazine. Above 86°F, the methanol in aspartame decays, forming formaldehyde and formic acid. When ingested, methanol attacks the eyes, CNS, and the gastrointestinal tract and can damage the liver and kidneys [25]. Formaldehyde and formic acid are corrosive to mucous membranes and can result in liver and kidney injury, and disease when ingested [25]. Formic acid is an established human toxin. Phenylalanine is believed to mediate or exacerbate hepatic encephalopathy [42, 43].

Chronic aspartame ingestion results in an increase of phase-I-metabolizing enzymes (CYP450) in laboratory animals [44]. Aspartame is a genotoxin, producing chromosome aberrations [45]. Recent research has shown it to be a multipotential carcinogenic agent for laboratory animals, even at a daily dose of 20 mg/kg of body weight, a level that is much less than the current acceptable daily intake [46].

There is published research on both sides of the toxicity question regarding aspartame, with almost equal numbers of papers claiming toxicity and safety. Most studies address controlled conditions where aspartame exposure could be localized. The foods people eat, however, are never restricted to ingestion of single species and mixture effects may indeed be responsible for the disparities of the test results. The differences in test results are believed to be due to ingestion of aspartame with varying other unidentified chemical species or quantities of other chemicals.

One study considered the toxicity of aspartame when coadministered with the food colorant, Quinoline Yellow (QY). In this study it was shown that synergistic effects are observed when these two additives are given together. Mouse neuroblastoma cells were induced to differentiate and grow neurites when the mixture of aspartame and QY was administered together. Inhibition of neurite outgrowth was found at concentrations of these additives theoretically achievable in plasma by ingestion of a typical snack and drink [47].

10.12 Non-Nutritive Chemicals in Food

Earlier sections addressed impurities allowed in food and examples of chemicals used to flavor and color food. Other xenobiotic chemicals are deliberately added to food during its preparation for preparation, esthetic, and storage purposes. The *Handbook of Food Additives* describes more than 8000 trade name and general chemical additives that are used in food products [48]. Those included are listed by category in Table 10.3.

10.13 The Bread We Eat

Clearly, all the additives listed in Section 10.6 are not present in any one food. An examination of the composition of ordinary white bread, however, reveals just how

Table 10.3 Categories of Food Additives Used in Food Preparation

Acidulents	Enzymes
Aerating agents	Fat replacements
Alkaline agents	Fermentation aids
Anticaking agents	Film-formers
Antimicrobials	Flavors
Antioxidants	Flavor enhancers
Antispattering agents	Gelling agents
Antistaling agents	Glazes
Aromatics	Humectants
Binders	Instantizing agents
Bittering agents	Leavening agents
Bleaching agents	Masticatory aids
Bodifying agents	Neutralizers/buffers/pH control agents
Bulking agents	Nutrients
Catalysts	Opacifiers
Clarifiers	Pickling agents
Clouding agents	Preservatives
Coatings	Propellants
Colorants	Raising agents
Color adjuncts	Release agents
Color diluents	Solubilizers
Color retention aids	Solvents
Cooling agents	Suspending agents
Curing agents	Sweeteners
Defoamers/antifoams	Synergists
Dietary fiber	Tenderizers
Dietary supplements	Texturizers
Dispersants	Thickeners
Dough conditioners	Vehicles
Drying agents	Viscosity modifiers
Egg replacements	Vitamins
Emulsifiers	Whipping agents
Encapsulants	

Source: Ref. [48].

many of these are found in the food we eat every day. Table 10.4 lists the ingredients of a commercially prepared white bread found in stores in the United States along with the ingredients of home-baked white bread prepared without chemical additives.

10.14 VOCs in Food

VOCs are present in almost all foods consumed in the United States. In a study by FDA scientists, 70 different foods were purchased repeatedly over a 5-year period

Table 10.4 Lists of Ingredients in Commercial and Home-Baked White Breads

Commercial White Bread	Home-Baked White Bread
Wheat flour	All-purpose flour
Barley malt	Butter
Ferrous sulfate (iron)	Sugar
B vitamins	Active dry yeast
Niacin	Salt
Thiamine mononitrate (B1)	Canola oil
Riboflavin (B2)	
Folic acid	
Water	
High fructose corn syrup or sugar	
Yeast	
Calcium sulfate	
Wheat gluten	
Soybean oil	
Salt	
Dough conditioners (may contain mono- and diglycerides sodium stearoyl lactylate dicalcium phosphate datem, sorbic acid and/or carbon dioxide)	
Vinegar	
Soy flour	
Tricalcium phosphate	
Yeast nutrients (may contain ammonium phosphate, monocalcium phosphate, calcium carbonatem, ammonium sulfate, ammonium chloride, and/or diammonium phosphate)	
Corn starch	
Wheat starch	
Enzymes	
Calcium propionate	
Whey	
Soy lecithin	

and analyzed for VOCs. Twenty-two VOCs were found in the foods tested, though no single VOC was found in all foods [49]. Table 10.5 lists the foods tested and Table 10.6 lists the 21 VOCs found in foods.

All of the chemicals listed in Table 10.6 are highly toxic and many have been associated with toxic effects of mixtures [50].

10.15 Chemicals in Food Packaging

Materials used to package food include paper, plastic, and rubber food wrappers and containers. These packaging materials contain monomers, oligomers, additives,

Table 10.5 Foods Analyzed for VOCs

Whole milk	Sweet rolls
American cheese	Chocolate chip cookies
Cheddar cheese	Sandwich cookies
Ground beef	Apple pie
Chuck roast	Milk chocolate candy bar
Bacon	Caramels
Hot dogs	Cola
Bologna	Low-calorie cola
Salami	Milk-based infant formula
Tuna	Beef, strained/junior
Fish sticks	Carrots, strained/junior
Eggs, scrambled	Apple juice, strained/junior
Peanut butter	Swiss cheese
Corn, cream style	Cream cheese
Popcorn	Chicken nuggets
White bread	Fried chicken, fast food
Blueberry muffins	Mixed nuts
Corn chips	Graham crackers
Fruit-flavored cereal	Butter crackers
Apples	French fried, fast food
Oranges	Quarter pounder/cheese
Bananas	Taco/tostado
Strawberries	Cheese pizza
Raisins	Cheese/pepperoni pizza
Avocados	Vanilla ice cream
Orange juice	Sherbet
Coleslaw	Popsicles
Tomatoes, raw	Chocolate snack cake
Potato chips	Cake doughnuts
Quarter pounder	Brownies
Meatloaf, homemade	Sugar cookies
Margarine	Sour cream
Butter	Olive/safflower oil
Vanilla ice milk	Fruit-flavored drink
Chocolate cake, commercial	Soy-based infant formula

Source: Ref. [49].

It should be noted that foods that are normally cooked, e.g., fruits and vegetables, were cooked as they would be in a domestic kitchen prior to analysis. Fast foods were obtained ready-to-eat and analyzed as purchased.

polymer degradation products, additives, and impurities. The chemicals in packaging materials are estimated to contaminate food about 100 times more than pesticides and other POPs [51, 96]. The contaminants that migrate from packaging into food include allergens, chemicals with estrogenic activity, specific organ toxins, genotoxins, and carcinogens. The following examples are illustrative.

Table 10.6 VOCs Found in Foods Over a 5-Year Period

Benzene	Ethylene dichloride
Bromodichloromethane	<i>n</i> -Propylbenzene
<i>n</i> -Butylbenzene	Styrene
Carbon tetrachloride	Tetrachloroethylene
Chlorobenzene	Toluene
Chloroform	1,1,1-Trichloroethane
Cumene	TCE
<i>o</i> -Dichlorobenzene	1,2,4-Trimethylbenzene
<i>p</i> -Dichlorobenzene	<i>m</i> - and/or <i>p</i> -Xylene
<i>trans</i> -1,2-Dichloroethene	<i>o</i> -Xylene
Ethyl benzene	

Source: Ref. [49].

1. It is estimated that about one-third of all food wrapping contains latex, to which as many as 6% of people are allergic [52].
2. Chemicals with known estrogenic activities contained in plastic and rubber food contact materials include bisphenol A, nonylphenol, benzybutyl phthalate, styrene oligomers, and hydroxylated benzophenones. It has also been found that chemicals in packaging, which either contain a phenol group in their structures or form one easily by hydrolysis or metabolism, also display estrogenic activities [53]. Hormone-disrupting phthalates also migrate from food packaging into food [54].
3. Polyethylene terephthalate (PET), which is widely used in water and other beverage containers, contains acetaldehyde and limonene, which can migrate into the packaged products [55]. PET absorbs organic compounds it comes in contact with and recycling may introduce contaminants upon reuse [56]. Contamination by recycling is of particular concern when the container has been used to hold cleaners or solvents prior to recycling.
4. Polymerization aids, including initiators and catalysts, have been found in plastics intended for food contact. Methyl benzoate, benzoic acid, biphenyl benzoate, phenyl benzoate, and azobisisobutyronitrile were among the chemicals detected in food [57].
5. Paper and board materials intended for food packaging have been found to contain a large number of toxic organic compounds in them. These include alkyl and aryl aldehydes, BHT, di-*tert*-butylphenol, and substituted benzophenones [58].
6. Perfluorochemicals are used in the manufacturing of food packaging materials and cookware. Perfluoro-octane sulfonate (PFOS) is a residual impurity in some paper coatings used for food contact. Perfluoro-octanoic acid (PFOA) is contained in nonstick cookware coatings. Recent epidemiological studies have shown that both PFOS and PFOA are widely present in human blood [59].
7. Microwave heat susceptors are packaged with foods intended for microwave oven preparation to generate high temperatures (greater than 300°F) to cook foods such as pizza and French fried potatoes. The metalized polyester film, adhesive, and paper packaging materials contained in these products release VOCs that are absorbed by the foods they package. The VOCs released include benzene, 1,1,1-trichloroethane, and 2-(2-butoxyethoxy)ethanol [60].
8. Printing inks and adhesives used in packaging frequently release VOCs through packaging layers into foods. In one of Harold Zeliger's (as yet unpublished) studies, it was discovered that amines used to catalyze adhesive curing between layers of polyethylene and polypropylene film in food packaging readily permeated through the film and contaminated the food.

10.16 Irradiated Food

Food may be preserved by irradiation with beams of ionizing radiation produced by radioactive isotopes. Such treatment kills certain bacteria and molds that induce spoilage. Though irradiated food is not left radioactive, it does break chemical bonds and generate free radicals with, at this time, largely unknown consequences. The safety of irradiated food is being addressed at this time, with some countries allowing it in the marketplace and others banning its sale [61]. Unsaturated lipids seem to be particularly vulnerable to irradiation. Irradiated almonds turned rancid upon irradiation with accelerated electrons at a dose of 10 kGy [62]. Irradiation of PET copolymers intended for food contact significantly increased concentration of acetaldehyde [63]. To date, the paucity of adequate research suggests caution in accepting irradiated food, particularly since the ingestion of food with increased numbers of free radicals can give rise to higher levels of reactive oxygen species and a higher cancer risk, as was discussed in Chapter 4.

10.17 Toxic Mixtures in Food

Very little published literature addresses the toxic effects of chemical mixtures in foods. A few have been referred to in the preceding text. Eight other examples follow here.

10.17.1 *2,3,7,8-Tetrachlorodibenzo-p-dioxin*

The ubiquitous environmental contaminant TCDD accumulates in animal fat and plant tissues. The food chain is the primary source of exposure to humans. TCDD is a multifaceted toxin that regulates the expression of a wide range of drug-metabolizing enzymes and impacts a large number of biological systems. The acute effects of TCDD exposure (including chloracne, porphyria, hepatotoxicity, and central and peripheral nervous system toxicity) are well described in the literature. Due to the long-term persistence of TCDD in the human adipose tissue, chronic effects may present as long as several decades after exposure. It is hypothesized that TCDD-induced atherosclerosis, hypertension, diabetes, and nervous system damage can be present long after initial exposures [64]. TCDD is slowly released from adipose tissue into the human bloodstream over a period of years to decades. By mixing with other xenobiotics that are taken up by the body long after the absorption of TCDD, new toxic mixtures are almost constantly being created. These mixtures have unknown effects on humans.

10.17.2 *Genotoxic Food Additives*

Many chemicals currently used as food additives are genotoxic. One study reports 39 different chemicals, including those that are colorants, preservatives, antioxidants,

fungicides, and sweeteners, are genotoxic to stomach, colon, liver, kidney, bladder, lung, brain, and bone marrow tissues in test animals [65].

10.17.3 Carcinogenic Flavorants

Fifteen flavorant compounds approved by the Flavor and Extract Manufacturers Association (FEMA) for the GRAS list have been found to be carcinogenic to laboratory animals. These include benzyl acetate, cinnamyl anthranilate, ethyl acrylate, and pyridine [66]. Though the author of the study concludes that the levels of these compounds found in foods are below the thresholds of carcinogenic concern, no consideration was given to the effects of mixtures, which have been shown to induce effects at lower concentration than individual compounds [50, 67].

10.17.4 Preservatives

The preservative BHT has been shown to have adverse effects on the liver and lungs [68, 69]. When mixed with another preservative, BHA, the BHA/BHT mixture enhances the lung toxicity. In another study, it was shown that BHA, eugenol methyl paraben, vanillin, guaiacol, ferulic acid, and other phenolic compounds used in food products enhanced the *in vitro* peroxidase-catalyzed covalent bonding of BHT to microsomal protein and the formation of BHT–quinone methide [70].

10.17.5 BHA and Marijuana

BHA has limited cytotoxic effects. When mixed with delta(9)-tetrahydrocannabinol (THC) (extracted from marijuana cigarettes), however, synergistic cytotoxicity to lung cells was observed. The study concludes that coexposure to marijuana smoke and BHA can promote deleterious health effects in the lung [71].

10.17.6 Recycled Food Packaging

Recycled paper products are used in food packaging. Such products contain 4,4'-bis(diethylamino)benzophenone, 4,4'-bis(dimethylamino)benzophenone, 4-(dimethylamino)benzophenone, and bisphenol A, which are genotoxic. These compounds, however, are found in foods in concentrations that are too low to account for the genotoxic effects found upon investigation [72]. The study fails to take into account the presence of other xenobiotics that would produce a mixture with enhanced genotoxicity.

10.17.7 Enzyme Inhibition

Xenobiotic food additives, drugs, and biologically active endogenous compounds can interact and affect body biochemistry. For example, dopamine sulfotransferase activity is strongly inhibited by the colorant tartrazine and flavorant vanillin, and vanillin, erythrosine B, and octyl gallate inhibit the sulfation of 17- α -ethinyl-estradiol, a xenobiotic steroid [73].

10.17.8 Nonionizing Radiation

Sunlight and other sources of nonionizing electromagnetic radiation can affect foods. For example, it has been shown that sodium nitrite, sodium nitrate, sodium benzoate, potassium sorbate, and benzoic acid exhibit additive photogenotoxic effects on *Escherichia coli*, causing increased mutations upon exposure to sunlight [74]. Such effects potentially increase the toxic risks associated with food additives.

10.18 Excipients in Pharmaceuticals and Vitamin and Mineral Preparations

Excipients are “inactive” ingredients in pharmaceuticals and vitamin and mineral preparations. These compounds, which often make up the majority of the mass or volume of oral and parenteral drug products, are considered to be inert and not affect the intended functioning of the active ingredients. Excipients, which frequently constitute the majority of the mass or volume of oral preparations, have a variety of purposes that include:

- Appearance
- Palatability
- Stability
- Affecting bioavailability
- Consistency.

Almost 800 chemicals have been approved by the FDA for use as inactive additives in drug products. Labeling regulations do not require that they be listed on product labels [75]. Table 10.7 lists the categories of pharmaceutical excipients in use [34].

Excipients are not foods, but many are the identical chemicals used as food additives, leading to multiple sources and increasing doses when foods, prescription drugs, and/or over-the-counter medications containing them are ingested at the same time. Though excipients are extensively used in inhalational, parenteral, and ophthalmic medications, the consideration here will be limited to ingestion. Effects of toxic inhalational, parenteral, and ophthalmic excipients are considered in subsequent chapters.

Many excipients have been associated with adverse reactions in those ingesting drugs and vitamin/mineral formulations containing these compounds [34, 76]: Antioxidants (e.g., sodium sulfite, sodium and potassium bisulfites, and metabisulfites), bacterial preservatives (e.g., benzyl alcohol and benzalkonium chloride), artificial sweeteners (e.g., aspartame and saccharine), coloring agents (e.g., FD&C Yellow No. 5, Blue No. 2, and Red No. 40), and propylene glycol. A few examples of the toxic effects of very commonly used excipients are as follows.

10.18.1 Sulfites

Sulfites are widely used as antioxidants to prevent spoilage. Ingestion of these, however, has been shown to produce severe adverse reactions including wheezing, dyspnea, and chest tightness in those with known reactive airway disease [77, 78].

Table 10.7 Categories of Pharmaceutical Excipients in Use

Aerating agents and gases	Levigating agents
Air displacement agents	Ointment bases
Color additives	pH control agents (acids, alkalis, and buffers)
Denaturing agents	Solvents and vehicles
Dispersing agents	Stiffening agents
Emollients	Suppositories
Emulsifiers and emulsifying salts	Surfactants
Flavors	Suspending agents
Fragrances	Tablet binders
Humectants	Tablet coatings

Source: Ref. [34].

10.18.2 Aspartame

Aspartame (described in Section 10.11) is used extensively in chewable and sugar-free drug formulations. The most common adverse effect attributed to aspartame use in drugs is headache [79]. Aspartame ingestion in drugs has also been anecdotally linked to neuropsychiatric disorders including panic attacks, mood changes, visual hallucinations, and manic attacks [80, 81].

10.18.3 Saccharin

Many liquid and solid oral drugs contain saccharin as a sweetener. Adverse effects resulting from pharmaceuticals include pruritus, urticaria, eczema, photosensitivity, prurigo, wheezing, nausea, diarrhea, tongue blister, tachycardia, headache, and sensory neuropathy [82–85].

10.18.4 Coloring Agents

Coloring agents are used in drugs to give recognizable identity to specific products and dosages and for appearance purposes. Several of these have been associated with adverse effects when used in drugs. FD&C Yellow No. 5 (tartrazine), FD&C Blue No. 2 (indigo carmine), and FD&C Red No. 40 are known to produce acute bronchospasm and anaphylactoid reactions [86–88]. Sunset yellow has been shown to be associated with abdominal pain, vomiting, and indigestion [89]. Artificial food colors present in drugs have been related to hyperactivity in children [27, 90].

10.18.5 Propylene Glycol

Propylene glycol is commonly used to solubilize drugs in topical, oral, and injectable medications. Cardiac arrhythmias, CNS depression, and seizures have been reported in children who have ingested liquid medications containing propylene glycol, and

contact dermatitis has been noted following the application of propylene glycol to skin and mucous membranes [34]. These effects will be discussed in subsequent chapters.

The examples just given demonstrate the toxicities of some excipients. These additives, however, can also adversely affect the bioavailability of drugs [91]. There is also evidence that adverse reactions attributed to “active” constituents of drugs (e.g., erythromycin) may indeed have been due to the excipients or to excipient/drug mixtures, rather than to the drug itself [92]. Formulators of drugs are permitted to change the excipients incorporated into the drugs without testing or notification. Accordingly, some adverse effects attributed to drugs that have previously been tried and tested must be studied carefully before conclusions are reached.

10.19 Summary

Food supplies are contaminated with environmental pollutants, pesticides, growth hormones, and antibiotics. Foods, as well as pharmaceutical agents, are further impacted by additives that are incorporated for esthetic, manufacturing, and storing purposes, rather than for nutritional properties. As a result, people worldwide are constantly ingesting toxic xenobiotics of largely unknown composition.

Acute toxic events resulting from ingestion of food that has either been environmentally contaminated or prepared with toxic additives, such as those described in the preceding sections, are less common than chronic exposure effects. Ascribing particular toxic effects to specific agents is often complicated, given the complexity of most diets. Though examples of toxic mixture effects have been shown in the preceding text, most toxic effects of mixtures are difficult to identify. For example, the combined effects of BHA and BHT have been noted where both were known to have been ingested simultaneously. It is quite possible, even probable, that one would unknowingly eat two foods, one containing BHA and the other BHT, develop symptoms and not be able to identify the sources of the toxins. Also, some reactions to foods can easily be misunderstood. For example, some people report an allergic reaction to chocolate following its ingestion. Some so-called chocolate-containing products, however, contain no chocolate whatsoever, using extracts and synthetic components to simulate the chocolate taste. In such cases, the symptoms that ensue are responses to unidentified stimuli.

Adverse reactions to foods are not always attributable to any one food or even mixture of ingredients in foods. Individuals can react to mixtures of xenobiotic chemicals arising from more than one food. Chemical A can be present in one food, while B, or C, or D, and so on can come from other foods, with the mixture(s) forming after ingestion of combinations of foods. Toxic chemical mixtures can also arise from a combination of food ingestion and environmental exposure(s) to different molecular species.

Finally, it should be noted that reactions to xenobiotics can be idiosyncratic and functions of one's state of being or health, as was discussed in Chapter 4.

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11 Chemicals In and Around the Home

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11.1 Introduction

People are exposed to numerous xenobiotics in and around the home. Many, if not most, of the exposures are to mixtures of chemicals. Chemical products that are used in the home are more likely to result in toxic exposures than those used in the workplace for the following three reasons:

1. People generally assume that the products marketed for home use are safe.
2. Warning requirements for consumer products are not as rigorous as those for industrial products and less attention is paid to such warnings.
3. Consumers, who are not required to be educated and trained on the safe use of toxic chemicals, as workers are, are more likely to abuse chemical products than commercial users are. Such abuse includes eschewing the use of protective equipment and mixing chemicals together.

Home-use exposures come from a wide variety of sources. These include the following categories:

1. Arts and crafts supplies
2. Automobiles and small engines
3. Cleaners and fresheners
4. Construction and maintenance materials
5. Fire retardants

Table 11.1 Arts and Crafts Categories That Contain Toxic Chemicals

Adhesives	Leather working products
Candle-making materials	Marker pens
Ceramics	Paints
Cleaners	Plasters
Collages	Sealants
Dyes	Soap-making chemicals
Fixatives	Solders
Furniture finishes	Stains
Glass etchers	Varnishes
Glazings	

- 6. Landscape and yard supplies
- 7. Personal care and cosmetic products
- 8. Pesticides
- 9. Pet-care products.

The U.S. National Institutes of Health have prepared a Household Products Database that provides toxicity information for a large number of household products. Included are product, ingredient, and material safety data sheet information for numerous individual products [1]. Another source of such information is Home Safe Home by D.L. Dadd [2].

11.2 Arts and Crafts

Those engaged in arts and crafts activities use many different toxic chemicals. Table 11.1 contains a partial list of arts and crafts materials that contain toxic chemicals.

Toxic chemicals commonly contained in arts and crafts materials are listed in Table 11.2 [3].

Most of the chemicals listed in Table 11.2 target the respiratory and central nervous systems. Exposures in arts and crafts use are almost always to mixtures of lipophilic and hydrophilic chemicals. When used in areas with poor air circulation (as is often the case in home use) unexpected acute toxicity can result [3]. For example, it has been reported that exposure to formaldehyde and terpene hydrocarbons at very low levels unexpectedly produced dyspnea and other lower lung symptoms in woodworkers. The effects could not be attributed to either formaldehyde or terpenes alone at low levels of exposure [4]. In another example, it was reported that chronic exposure to a combination of very low concentrations of MEK, ethyl acetate, and aliphatic hydrocarbons in a leather-adhesive formulation induced unanticipated CNS effects [5]. Some products that are considered by most to be benign contain toxic chemical mixtures. Marker pens contain mixtures of methanol, ethanol, propanols, butanols, butyl acetate, and MIBK. Though such markers are labeled as “nontoxic,”

Table 11.2 Toxic Chemicals Commonly Contained in Arts and Crafts Materials

Acetone	Isocyanates
Acrylic monomers and oligomers	Isopropyl alcohol
Aliphatic hydrocarbons	MEK
Aromatic hydrocarbons (including toluene and xylene)	Methyl isobutyl ketone
Ammonia	Methylene chloride
Chlorine	Organic peroxides
DMF	Pigment dusts
Dimethyl sulfoxide (DMSO)	Silica
Ethyl benzene	Toluene
Ethyl acetate	1,1,1-Trichloroethane
Ethyl alcohol	Xylene
Formaldehyde	

Table 11.3 Chemical Products Used in Automobiles and Other Gasoline-Powered Machines In and Around the Home

Antifreeze	Motor oil
Battery acid	Power steering fluid
Brake fluid	Transmission fluid
Cleaning compounds	Waxes
Gasoline	

exposures to emissions from them have been shown to produce respiratory and neurological reactions in animals and humans, though the effects could not be attributed to any of the individual chemicals [6].

11.3 Automobiles and Small Engines

Gasoline-powered motors used in and around the home include automobiles, off-the-road vehicles, lawn mowers, electrical generators, boat motors, chain saws, weed wackers, snowmobiles, motorcycles, and snow blowers. In addition to gasoline, these machines have many other toxic chemical-containing products associated with their use. A representative list of these is given in Table 11.3.

A partial list of the chemicals contained in these products is given in Table 11.4.

Most of the chemicals listed produce vapors that target the respiratory and central nervous systems. All are dangerous if ingested and all are irritating or corrosive to dermal and eye tissues [7]. Mixtures of either alkalis or acids with lipophilic solvents (e.g., toluene, aliphatic hydrocarbons) produce enhanced burn effects [8]. Skin and eyes exposed to chemicals that can burn require aggressive treatment, particularly where alkalis are involved, to prevent progressive burning [9]. Home use of chemicals that cause burns is responsible for many hospital admissions for advanced burn

Table 11.4 Partial List of Toxic Chemicals Contained in Automobile and Small Engine Products

Aliphatic hydrocarbons	Methanol
Aromatic hydrocarbons (including benzene, toluene, and xylene)	Polynuclear aromatic hydrocarbons
Carbon monoxide	Silicones
Diethyl ether	Sodium hydroxide
Ethanol	Sulfuric acid
Ethylene glycol	Surfactants
Formaldehyde	1,1,1,2-Tetrafluoroethane
Glycol ethers	

treatment of eyes and skin. Mixtures of lipophiles and hydrophiles listed in Table 11.3 have been shown to produce unanticipated toxic effects. For example, mixtures of formaldehyde, ethanol, and aromatic hydrocarbons induce respiratory and neurotoxic effects in humans [10].

11.4 Cleaners and Fresheners

Large quantities of chemical products are used to clean, freshen, and disinfect homes. Table 11.5 shows a representative list of these products.

Toxic chemicals contained in cleaning, freshening, and disinfection products are listed in Table 11.6.

All the chemicals listed in Table 11.6, with the exception of the surfactants, are volatile and attack the respiratory system upon inhalation. All readily defat and attack the skin. It is not implied here that these products are unsafe to use. The real danger for these products arises when they are ingested or mixed. The following examples illustrate the dangers of mixing:

1. Drain cleaners are generally one of two types—sodium hydroxide or sulfuric acid. Numerous accidents have occurred when users have first applied one, and, when it did not clear the drain, subsequently applied the other. The neutralization reaction of sodium hydroxide and sulfuric acid generates a large quantity of heat, sufficiently large to rapidly heat water present to its boiling point and result in a violent eruption. Numerous individuals have suffered eye and skin burns because of unreacted sodium hydroxide or sulfuric acid that has thus erupted following the mixing of these two chemicals.
2. Many people mix cleaners to their peril. Mixing of bleach (sodium hypochlorite) with ammonia results in the generation of mono-, di-, and tri-chloramines, as shown in Figure 11.1.

Chloramines are toxic to the respiratory system, with asthma and chronic bronchitis resulting from repeated exposures [11, 12]. In an exposure event I investigated, a woman poured a mixture of ammonia and bleach into a toilet bowl. She experienced respiratory failure and death when she inhaled the resultant fumes.

Table 11.5 Representative List of Chemical Products Used in the Home for Cleaning, Freshening, and Disinfection

Air fresheners	Degreasers
Anti-static sprays	Disinfectants
Bleach	Metal polishes
Carpet shampoos	Quaternary ammonium salts
Cleaners	Spot and stain removers
Dishwashing	Tile and grout cleaners
Drain	Waxes
Hard-surface cleaners	Wood treatments
Laundry detergents	
Window cleaners	

Table 11.6 Toxic Chemicals Contained in Cleaning, Freshening, and Disinfection Products

Acetone	Oxalic acid
Aliphatic hydrocarbons	Phosphoric acid
Ammonia	Sodium hydroxide
Chlorine	Sodium metasilicate
Butanes	Sulfuric acid
Glycol ethers	Surfactants
Hydrochloric acid	Tetrachloroethylene
Methylene chloride	1,1,1-Trichloroethane
Monoethanol amine	

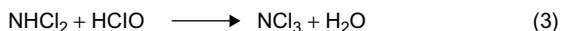
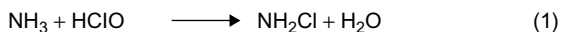


Figure 11.1 Mixing of bleach (sodium hypochlorite) with ammonia results in the generation of mono-, di-, and tri-chloramines.

11.5 Maintenance Materials

The construction and maintenance materials used by home residents are identical to those used commercially by safety-trained professionals. Whereas professional users are required to undergo training for the safe use of hazardous chemical products, home users are under no such constraint. As a result, people are exposed to numerous toxic exposures in the home. A representative list of products containing toxic

Table 11.7 Home-Use Maintenance Products Containing Toxic Chemicals

Adhesives	Pigment powders
Blacktop sealants	Pipe cements
Caulks	Plasters
Fertilizers	Plywood
Joint compounds	PVC
Lacquers	Portland cements
Lubricants	Sealants
Paint thinners	Septic tank additives
Paints	Swimming-pool chemicals
Particle board	Varnishes

Table 11.8 Representative List of Toxic Chemicals Contained in Home-Use Maintenance Products

Alkalies	Glycol ethers
Aliphatic hydrocarbons	Methylene chloride
Amine epoxy catalysts	Polynuclear aromatic hydrocarbons
Ammonia	Styrene
Chlorine	Toluene
Dibutyl phthalate (and other phthalates)	Toluene diisocyanate (and other isocyanates)
Ethylene glycol	1,1,1-Trichloroethane
Formaldehyde	Xylene

chemicals that are regularly used in home maintenance projects is shown in Table 11.7.

A representative list of toxic chemicals contained in home-use maintenance products is given in Table 11.8.

Most household maintenance products contain mixtures of lipophiles and hydrophiles that can produce unanticipated toxic effects. Irritant-induced asthma is an example of such an effect. Solvent-based and water-borne paints contain solvents that are non-sensitizing irritants which individually are not known to induce asthma. Despite this, exposures to both types of paints have been shown to cause the asthma-like condition, RADS [13, 14]. RADS is discussed in detail in Chapter 17.

11.6 Brominated Flame Retardants

Brominated flame retardants (BFRs) are compounds widely used to impart fire-retardant properties to textiles, plastics, and electronic equipment. They are incorporated into many household products including children’s pajamas, upholstery fabrics, polyurethane (PU) foams (furniture cushion padding), construction materials, electrical equipment, and personal computers.

The following are some of the BFRs currently in use:

- Tetrabromobisphenol-A (TBBTA)
- Hexabromocyclododecane (HBCD)
- PBBs
- PBDEs.

These compounds serve as flame retardants because the relatively weak carbon–bromine bonds in them are readily broken when heated. Thermal energy releases bromine radicals that couple with carbon radicals produced in fires to decrease flame sizes, thereby reducing heat and lowering carbon monoxide production [15]. They are similar in structure to PCBs and are resistant to environmental degradation.

The PBDEs are of particular concern. They are incorporated into polymer matrices, but are not covalently bonded and readily leach out of substrates holding them. These compounds are similar in structure to PCBs, are persistent organic pollutants (POPs), and are resistant to environmental degradation and metabolism. They can be absorbed via inhalation, ingestion, and dermal contact. The less-brominated PBDE species (tetra-, penta-, and hexa-moieties) have been found in human blood, adipose tissue, and breast milk. These bioaccumulate in human adipose tissues [16].

Many PBDE mixtures are banned by the European Union (EU), but are still in use in the United States. As a result, PBDE levels in breast milk from North American mothers is at least an order of magnitude higher than that in breast milk from European women [17].

PBDEs are estrogen disruptors and neurotoxins. They are believed to cause thyroid and neurodevelopmental effects. Short-term exposure to PBDEs interferes with thyroid function and disrupts hormonal balance [18]. Additive thyrotoxic effects were observed when PBDEs were administered to laboratory animals along with PCBs or chlorinated hydrocarbons [19]. PBDE exposure has been linked to neurodevelopmental dysfunctions in children and young adults [20, 21]. Administration of PBDE to 10-day-old laboratory animals resulted in impaired spontaneous motor behavior, affected learning and memory, and permanent behavioral effects [21]. In vitro exposure of PBDE to human breast cancer cells demonstrated estrogenic potencies [22].

PBDEs are alleged human carcinogens. Several studies have demonstrated an association between adipose tissue PBDE levels and non-Hodgkin lymphoma [23, 24].

Studies on the effects of mixtures of PBDEs and other toxicants are sparse. A recent study, however, has demonstrated that PBDE affects the cholinergic system and might be expected to interact with other environmental toxins [25].

11.7 Personal Care and Cosmetic Products

Many personal care and cosmetic products contain toxic chemicals. Categories of products containing toxicants are listed in Table 11.9.

A partial list of the toxic chemicals contained in the products listed in Table 11.9 is shown in Table 11.10.

Table 11.9 Personal Care and Cosmetic Products Containing Toxic Chemicals

Bath and shower soaps and cleaners	Lip balms
Eye, facial, and body makeup	Nail care
Fragrances	Oral hygiene
Hair care	Shampoos
Hair colorants	Skin care
Hair-loss treatments	Sunscreen
Hormonal creams	

Table 11.10 Partial List of Toxic Chemicals Contained in Personal Care and Cosmetic Products

Aliphatic hydrocarbons	Lithium carbonate
Ammonium, sodium, and potassium thioglycolates	Metal oxides
BHA	Methyl and propyl paraben
BHT	Organic peroxides
Artificial food colors (FD&C colorants)	Phenacetin
Artificial sweeteners (aspartame and saccharine)	Phenolphthalein
Benzophenone	Polyethylene glycol
Carboxylic acids	Polymers
Cetyl alcohol	Potassium dichromate
Dibutyl phthalate	Propylene glycol
Ethanol	Quaternium ammonium salts
Formaldehyde	Surfactants (sodium lauryl sulfate and other ionic and nonionic species)
Fragrance compounds (see Table 11.11)	Thioglycolates
Hydrogen peroxide	Toluene
Lead acetate	

In addition to those listed in Table 11.10, a large number of the chemicals listed on the FDA GRAS and EAFUS lists (see Section 10.7) are also contained in personal care and cosmetic products. Cosmetic products in particular have come under close scrutiny in the EU, which has far more stringent labeling requirements than those in the United States.

Many cosmetics are formulated with inorganic and organic compounds that are toxic to skin and eyes, when inhaled or ingested. Some of these compounds, e.g., propylene glycol, have been identified as sensitizers following long-term exposure [26]. Formaldehyde, BHA, phenolphthalein, potassium dichromate, and lead acetate are considered to be carcinogenic [27]. Lithium carbonate and toluene are teratogens [27]. Dibutyl phthalate affects reproduction [27]. Pigments composed of inorganic minerals and organic binders, organic dyes (e.g., azo dyes), and fragrances are known to cause ACD upon skin contact [28]. Hair-treatment products contain several sensitizing compounds (including ammonium thioglycolate) [29] and corrosives (such as sodium hydroxide) [27].

Table 11.11 Fragrance Ingredients that Require Labeling, Which Cause Allergic Reactions, Contact Dermatitis, or Asthma in Sensitized Individuals

Amyl cinnamal	Benzyl alcohol
Cinnamyl alcohol	Citral
Eugenol	Hydroxycitonellal
Isoeugenol	Amylcinnamyl alcohol
Benzyl salicylate	Cinnamal
Coumarin	Geraniol
Hydroxyisohexyl-3-cyclohexene	Carboxyaldehyde
Anise alcohol	Benzyl cinnamate
Farnesol	Butyl methylpropional
Linalool	Benzyl benzoate
Citronellol	Hexyl cinnamal
D-Limonene	Methyl-2-octynoate
Alpha-isomethyl ionone	<i>Evernia prunastri</i> extract

Chemical mixtures in cosmetics give rise to enhanced toxicity, low-level toxicity, and unexpected target organ attack. Cosmetic products are composed of many lipophilic and hydrophilic chemicals. Numerous instances of “strange” injuries, including chemical burns, skin and respiratory sensitization, from the use of cosmetic products have been documented in which the injuries sustained could not be accounted for by a consideration of the individual chemicals involved [30].

The exact chemical composition of fragrances need not be identified under FDA regulations in the United States. The EU Seventh Amendment regulation, however, requires the labeling of fragrance ingredients which can cause allergic reactions, contact dermatitis, or asthma in sensitized users [31]. Currently, 26 fragrance ingredients require such labeling. These are listed in Table 11.11.

No such federal regulation is currently in force in the United States, though the California Safe Cosmetics Act of 2005 requires the identification and labeling of toxic chemicals in cosmetics.

EU regulations also ban the use of three classes of toxic chemicals which either

1. pose risks of cancer,
2. cause endocrine (hormonal) or reproductive disturbances, or
3. cause genetic damage.

The California Safe Cosmetics Act of 2005 does not ban such chemicals but requires their labeling on cosmetic products sold after January 1, 2007. The California regulation derives the list of cosmetic chemicals requiring labeling from its Proposition 65 (PROP 65) list of approximately 750 chemicals known to cause cancer or reproductive toxicity [32]. A partial list of the PROP 65 chemicals used in cosmetics is given in Table 11.12.

ACD is related to cosmetic contact in many instances [33–35]. ACD has been shown to arise from contact with different types of cosmetic products. These include:

1. Perfumes and their ingredients, e.g., benzaldehyde, cinnamic aldehyde, linalool, and terpenes [36, 37].

Table 11.12 Partial List of Chemicals Used in Cosmetics
Requiring Labeling Under the California Safe
Cosmetics Act of 2005

Acid blue #3	Iodine
Acid yellow #3	Lead acetate
Acrylamide	Lidocaine
BHA	Lithium carbonate
Coal tar	Mercury
Dibutyl phthalate	Petroleum
D&C blue #6	Phenacetin
Diethanolamine	Phenolphthalein
Dimethylamine	Selenium sulfide
Ethyl acrylate	Talc
FD&C red #3	Tetrahydrozoline HCl
Formaldehyde	Toluene
Hexachlorophene	Zirconium silicate

2. Polymers, e.g., polyvinylpyrrolidone/hexadecene copolymer in lipstick [38] and phthalic anhydride/trimellitic anhydride/glycols copolymer in nail polish [39].
3. Preservatives, e.g., *p*-chloro-*m*-xylenol used in cosmetics and as an active ingredient in antimicrobial soaps [40].
4. Surfactants, e.g., cocamidopropyl betaine, commonly used in rinse-off cosmetic products [41].

Mixtures play a large role in personal care and cosmetic product toxicities. Several studies illustrate this.

1. Sodium myristoyl sarcosinate and sodium myristate alone do not cause ACD, yet a mixture of the two chemicals does [42].
2. Coumarin is a component of cosmetics and fragrances for which conflicting results have been reported regarding its propensity to induce contact allergy. A careful study has shown that pure coumarin does not exhibit irritant or sensitizing properties. It only exhibits toxic properties when contaminated with impurities [43].
3. Dexpanthenol (the alcohol corresponding to vitamin B5) and cocamidopropyl PB dimonium chloride phosphate (a phospholipid derived from coconut oil) are common ingredients in many cosmetics and soaps which individually are not known to cause ACD. Mixed together in a facial hydrating lotion, however, they have been shown to produce ACD [44].
4. Photoallergic responses to sunscreen products represent an area where chemical components not known to produce dermal allergic responses are activated by solar radiation to produce ACD [45, 46]. It is hypothesized here that in these instances, electromagnetic radiation may activate the skin to adsorb and/or absorb species that do not so react without the incident radiation. Alternatively, the molecular species themselves are excited by the radiation to molecular states that make them more reactive to skin. Chemicals exhibiting photoallergic contact dermatitis include oxybenzone, butyl methoxy dibenzoylmethane, methoxycinnamate, and benzophenone, all molecules that are readily photoexcited [45].
5. Fragrance products (cologne and toiletwater) containing mixtures of aldehydes, esters, terpenes, and carboxylic acids were found to induce acute respiratory and neurotoxic effects

Table 11.13 Household Products Containing Pesticides

Animal repellents	Fungicides
Animal shampoos	Herbicides
Flea and tick control products	Insect repellents
Fly sprays for horses	Insecticides
Fumigants	Rodenticides

in laboratory animals. These effects were not predicted from a consideration of the toxicities of the individual chemicals in the amounts present [47].

11.8 Pesticides

Pesticides are used in and around the home in numerous ways. Table 11.13 contains a representative list of products containing pesticides.

The toxicities of pesticides will be discussed in detail in Chapter 14.

11.9 Other Mixture-Containing Products

The sources of xenobiotics discussed in the preceding sections are the most prevalent ones. There are numerous others, however. Building materials of construction and furnishings are sources of respiratory, nervous system, and dermal toxins. These will be discussed in detail in Chapter 12. Tobacco smoke is responsible for many health effects in human, to both smokers and nonsmokers who are exposed to its toxins. The effects of tobacco smoke will be discussed in detail in Chapter 15.

Air fresheners emit aliphatic and aromatic hydrocarbons, ethyl butyrate, *m*-methoxybenzaldehyde *N*-methylformamide, and other compounds that together are pulmonary irritants and induce behavioral abnormalities [48].

Mattress covers emit mixtures of aromatic hydrocarbons, TCE, and phenol, the mixture of which induces acute respiratory effects including asthma-like reactions [49]. Similar effects are observed with emissions from disposable diapers [50], though such responses are not predicted from the measured concentrations of the chemicals.

11.10 Summary

Exposures to single toxic chemicals in and around the house produce many well-known identifiable effects in people. An example of such an effect is respiratory irritation following inhalation of chlorine bleach fumes. Often, individuals develop clinical symptoms that are associated with mixtures of chemicals, for example headache and dizziness following inhalation of paint fumes containing toluene and glycol ethers.

At times, people react acutely or chronically to unknown stimulants. In such cases, it is hypothesized that unidentified mixtures are often the causative agents. Such toxic mixtures can arise from mixtures of two or more household products as well as from the mixture of household chemicals with chemicals from foods, outdoor air pollutants, water pollutants, or industrial chemicals that are carried into the home on the clothing of workers. In many of these mixture exposure instances, the health effects cannot be attributed to any of the individual chemicals present, but produce distinct clinically defined symptoms.

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12 Sick Building Syndrome

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12.1 Introduction

Sick Building Syndrome (SBS) is a term that connotes different meanings. Originally used to infer a broad range of respiratory and CNS symptoms and environmental discomfort [1], it now generally denotes mucous membrane irritation (including nose, throat, and eye irritation), respiratory discomfort (including chest discomfort), skin symptoms (including itching, dryness, and erythema), sensory irritation (primarily odor), and other symptoms. “Sick” buildings are most commonly office structures, but other buildings, including warehouses, stores, and peoples’ homes, can also be places where SBS is found.

Table 12.1 Symptoms Associated with SBS

Abdominal pain	Lethargy
Aching joints	Nasal congestion
Chills	Nausea
Cough	Queasiness
Diarrhea	Rapid heartbeat
Difficulty wearing contact lenses	Rash
Disorientation	Runny eyes
Dizziness	Runny nose
Dyspnea	Shortness of breath
Earache	Sinus pain
Eczema	Sneezing
Facial itch	Sore throat
Facial rash	Stuffy nose
Fatigue	Throat dryness
Fever	Tongue/lip numbness
Impaired memory	Trouble sleeping
Itchy eyes	Swollen eye lids
Itchy hands	Weight loss
Headache	Wheezing
Hoarseness	

SBS has been associated with airborne biological and chemical components, including bioaerosols, VOCs released from building materials and furnishings, personal use products (e.g., perfumes), and environmental tobacco smoke (ETS) [2].

12.2 SBS Symptoms

Many studies have been carried out to identify the symptoms associated with SBS. References [3–6] are representative of these. Table 12.1 was compiled from these and other sources as well as from the experiences of this writer with SBS. It should be noted that the symptoms listed in Table 12.1 are composites of many reports. All are not found at any one site. Also, though the symptoms are those self-reported by the occupants of the “sick” buildings surveyed, they have been given credence because multiple individuals, often without contact with one another, have reported identical symptoms.

12.3 Contributory Sources of SBS

Buildings that are tightly insulated or hermetically sealed to retain heating or cooling often have limited air exchanges and retain pollutants that are released into the air. Many building components and products used in buildings are sources of SBS-producing symptoms [7]. Table 12.2 contains a list of these.

Table 12.2 Sources of SBS

Adhesives	Infectious agents
Carpeting	Lead
Cigarette smoke	Molds and mildew
Cleaning solvents	Paints
Combustion of fuel	Paper products
Copier solvents	Personal care products
Dust mites	Pesticides
Fiberboard	Plastics
Fiberglass	Plywood
Furnishings	Resins

12.4 VOCs in Buildings

Buildings that are tightly insulated or hermetically sealed to retain heating or cooling often have limited air exchanges and retain VOCs that are released into building interiors by materials of construction, furnishings, adhesives, paints, cleaners, combustion fumes, copier toners, and personal products. VOCs can also enter building interiors from outdoor sources such as air-conditioning intakes. Approximately 1000 different VOCs have been identified in indoor air [8–10]. Table 12.3 contains a partial list of these.

12.5 Paint

Paints currently used for indoor application are now almost exclusively waterborne. Most of these fall into the following categories [11]:

- Acrylic latex paint (flat and semigloss)
- Latex enamel
- Latex wall paint
- Latex heavy-bodied wall paint
- Latex primer
- Sealing paint.

In addition to water, these paints contain biocides, surfactants, pigments, monomers, coalescing solvents, driers, and volatile additives [3, 12]. Volatile components contained in these include aldehydes, aliphatic hydrocarbons (straight chain and cyclic), aromatic hydrocarbons, esters, ethers, glycol ethers, glycol ether esters, and halogenated hydrocarbons. Some of these materials are listed in Table 12.4.

Exposure to waterborne paints is known to induce acute and chronic dermal, respiratory, and CNS effects [11]. All the chemicals listed in Table 12.4 are individually toxic [13] and mixtures of many of these are known to induce unanticipated toxic effects in humans [14].

Table 12.3 Partial List of VOCs Found in Indoor Air

Acetic acid	Formaldehyde
Acetone	Heptane
Acrylamide	<i>n</i> -Hexanal
Acrylonitrile	<i>n</i> -Hexane
Ammonia	1-Hexanol
Aniline	Methacrylic acid
Benzene	3-Methyl-2-butanone
2-Butanone	4-Methyl-2-pentanone
2-Butoxyethanol	Methylene chloride
<i>n</i> -Butyl acetate	Naphthalene
<i>n</i> -Butyl acrylate	<i>n</i> -Nonane
2-Butyloctanol	<i>n</i> -Octane
Carbon monoxide	1-Octene
Chloroform	<i>n</i> -Pentanal
Cyclohexane	<i>n</i> -Pentane
Dichlorobenzenes	α -Pinene
1,1-Dichloroethane	Styrene
Dimethyl phenols	Tetrachloroethylene
Decane	Toluene
1-Decene	TDI
Dodecane	1,1,1-Trichloroethane
Ethoxyethyl acetate	TCE
Ethyl acetate	Vinyl acetate
Ethyl benzene	Xylenes
Ethylene oxide	

Table 12.4 Volatile Components Contained in Waterborne Paints

Acrylamide	Diethylene glycol monobutyl ether acetate
Acrylic acid	Diethylene glycol monomethyl ether
Acrylonitrile	Formaldehyde
Ammonia	Hexanal
1-Butoxy-2-propanol	Hydrocarbon mixtures
Butyl acetate	Methyl cyclohexane
Butyl acrylate	Methyl nonane
Butyl butyrate	Nonanal
Butyl methacrylate	Styrene
2-Chloroethyl acetate	Toluene
Dibutyl ether	2,2,4-Trimethyl-1,3-pentanediol mono-isobutyrate (Texanol)
Diethyl benzenes	Vinyl acetate

Wood stains and varnishes used indoors contain aliphatic and aromatic hydrocarbons, isocyanates, ketones, and esters. Though these have limited use compared with paint, newly finished building interiors often contain toxic levels of these. TDI, used as a catalyst in PU wood finishes, is a powerful respiratory irritant and sensitizer [13].

12.6 Environmental Tobacco Smoke

It is well established that many of the toxic effects of inhaling ETS (secondhand smoke) are identical with those of active smoking. ETS is associated with increased risk of lung cancer [15], respiratory disease (including asthma in children) [16], and cardiovascular disease (including acute myocardial infarction) [17].

The toxic effects of tobacco products will be discussed in detail in Chapter 15. It should be noted here, however, that combustion of tobacco indoors produces numerous VOCs that are also released by other sources of SBS [18]. These toxins include:

- Acetone
- Ammonia
- Aniline
- Benzene
- Carbon monoxide
- Formaldehyde
- Toluene.

These compounds may combine with other indoor environmental chemicals to produce additive and synergistic effects. For example, the combination of very low levels of formaldehyde (e.g., from tobacco) and terpenes (e.g., from cleaning products) produce dyspnea and other respiratory problems not observed from such levels of formaldehyde and terpenes alone [19].

12.7 Carpets

Carpets can be a major source of VOC emissions in residential, public, and commercial settings. Most carpet is composed of a synthetic pile (such as nylon or polyolefinic material) that is tufted through a primary backing coated with adhesive. The tufted pile is then set into a backing made of either styrene-butadiene rubber (SBR) latex, PVC, or PU that is sandwiched between the primary and secondary backings. The backings are typically made of woven polypropylene or jute. The chemical composition of carpet varies, depending upon the nature of the fiber, bonding materials, backing adhesives, dyes, dye solvents, antistatic and antistain treatments, fire retardants, pesticide, and fungicide applications [20, 21]. Carpet pads or application adhesives are typically used when carpet is put down, and these materials may also emit VOCs. Most carpet pads are PU materials. Some are made from virgin material, while others incorporate recycled PU.

Carpets emit a variety of VOCs depending upon their chemical compositions. SBR-backed carpets primarily emit 4-phenylcyclohexene (4-PCH), the chemical identified with “new carpet” odor, and styrene. PVC-backed carpets primarily emit formaldehyde, vinyl acetate, 1,2-propanediol, and 2-ethyl-1-hexanol. Carpets with a PU backing primarily emit BHT. Carpet emissions of VOCs are most pronounced immediately after new carpet is laid, with emission rates falling off rapidly as a function of

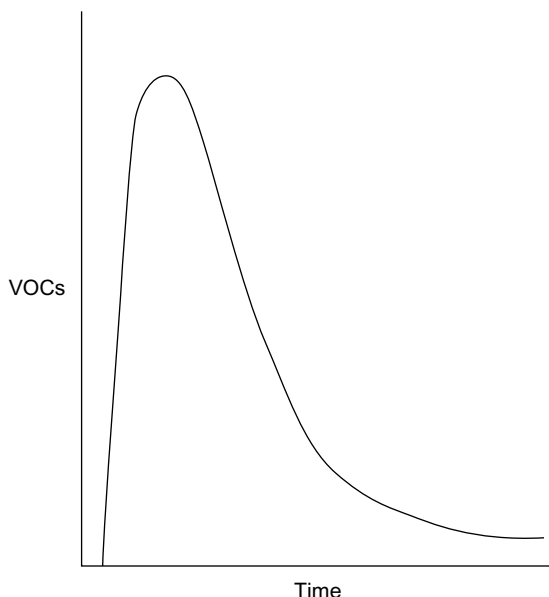


Figure 12.1 Typical curve of VOCs emitted from newly laid carpet as function of time. Actual values are functions of VOC content and temperature. This curve is intended only to demonstrate the shape of a typical example of carpet VOC emissions.

time, as depicted in Figure 12.1. Even though emission rates fall off rapidly, sensitized individuals often continue to exhibit symptoms for long periods of time.

Carpet emissions vary widely, even within carpets taken from the same lot. Often, particularly in a home setting, two or more different carpets are laid at the same time, making it difficult to ascribe toxicological effects to a particular carpet. This is particularly so when a central forced air system is used to heat or cool a home or office building. More than 100 compounds have been identified as carpet emission products. Table 12.5 lists VOCs typically emitted from new carpets [22, 23].

Of the compounds listed in Table 12.5, the following, in decreasing order of occurrence, are the most prevalent [23]:

- Styrene
- 4-Phenylcyclohexane
- 4-Vinylcyclohexene
- Undecane
- Propyl benzene
- Decane
- Ethylbenzene
- 2-Butoxyethanol
- Isopropylbenzene
- 1-Ethyl-3-methylbenzene
- Toluene
- p*-Xylene.

Table 12.5 VOCs Typically Emitted from New Carpets

Acetaldehyde	1-Ethyl-3-methylbenzene
Acetic acid	1-Ethyl-4-methylbenzene
Acetone	Ethyl-methyloctane
Benzaldehyde	Formaldehyde
Benzene	3-Hexenetrinitrile
1-Butanol	Isopropylbenzene
2-Butoxyethanol	Limonene
BHT	Methyldecane
Butylpentylcyclopropane	Methyldodecane
Caprolactum	2-Methyl-1-propene
Cyclobutane	Methyl-propylbenzene
Cycloheptane	Methyl-propylcyclohexane
1,3,5-Cycloheptatriene	Methylundecane
Cyclohexanol	4-Phenylcyclohexane
Cyclohexanone	β -Pinene
Decane	1,2-Propanediol
1,4-Dichlorobenzene	<i>n</i> -Propanol
Diethylcyclohexane	Propylbenzene
Dimethylcyclo-octane	Propylcyclopentane
Dimethyldecane	Propyldecane
Dimethylpentene	Styrene
Dimethylundecane	Tetradecane
Dimethylundecene	Toluene
Dipropylene glycol methyl ether	1,1,1-Trichloroethane
Dodecane	1,2,3-Trimethylbenzene
1-Dodecanol	Trimethylcyclopentane
4-Ethenylcyclohexane	2,2,5-Trimethylhexane
Ethylbenzene	Trimethylsilanol
Ethylcyclobutanone	Undecane
Ethyl-dimethylcyclohexane	Vinyl acetate
Ethylhexanol	4-Vinylcyclohexene
2-Ethyl-1-hexanol	Xylenes (<i>o</i> , <i>m</i> , <i>p</i>)
1-Ethyl-2-methylbenzene	

The hydrocarbons (all of the above except 2-butoxyethanol) are all neurotoxic [20]. 2-Butoxyethanol targets the respiratory system, liver, kidneys, lymphoid system, and blood [13]. Some studies have reported that new carpet VOC emissions are sufficiently low to not adversely affect indoor air quality nor impact the human respiratory system or CNS [20, 24]. Other studies, however, have reported that human exposures to new carpet emissions at very low concentrations of both the individual chemicals and total VOCs do induce serious respiratory system and CNS effects [25, 26]. The diametrically opposite conclusions reached by the two sets of studies can be attributed to a failure on the part of one set of studies (those which concluded that no toxic effects could be attributed to carpet emissions) to consider the effects of mixtures. The no-effect studies considered only the concentrations of the individual compounds emitted.

Table 12.6 Indoor Use Products That May Contain Formaldehyde

Adhesives—glues, pastes, and cements
Carpets
Ceiling tiles
Cleaners—rug, carpet, tile, toilet, window, and brush
Detergents
Deodorizers
Disinfectants
Dry-cleaning and spotting fluids
Dyes and inks
Floor coverings—linoleum and vinyl tile
Fuel combustion—natural gas and kerosene
Fumigators
Furniture
Insulation (urea formaldehyde)
Latex rubber—gloves and sheets
Medicines
Melamine
Paints—wall paint, lacquers, and varnishes
Paper—grocery bags, waxed paper, facial tissues, paper towels, and sanitary products
Personal care—deodorants, shampoos, cosmetics
Polishes—floor, shoe, furniture, and suede
Textiles—upholstery, wrinkle resisters, and permanent press clothing
Tobacco smoke
Toothpaste
Wood—plywood, particle board, veneers, decorative paneling

The studies that considered mixtures empirically found respiratory system and CNS effects from exposures to low-level carpet emissions [14, 27]. Another consideration is the temperature that carpet is exposed to. The amounts and the nature of VOCs emitted from carpets (as well as from paints, tiles, woods, and other materials) are temperature dependent. Higher temperatures not only accelerate the release of volatiles, but also result in the release of compounds not emitted at lower temperatures [28].

12.8 Formaldehyde

Formaldehyde is a major contributor to many “cases” of SBS. It is a very toxic chemical that is corrosive to the skin, eyes, and the respiratory system. Acute or chronic exposure can result in difficulty breathing and even brief exposures can induce asthmatic reactions in sensitized individuals [13]. Exposures to mixtures of formaldehyde and lipophilic chemicals can result in unanticipated toxic effects [14]. Formaldehyde is an animal carcinogen, a suspected human nasal cancer carcinogen [29], and suspected human leukemogen [30].

There are numerous sources of formaldehyde in indoor air. It is widely used as a preservative in products that are subject to attack by micro-organisms. These include many household products, among which are papers, cleaning products, furnishings, insulations, and cosmetics [31]. Table 12.6 lists indoor use products known to contain formaldehyde.

Mixtures of formaldehyde with other VOCs, including aliphatic and aromatic hydrocarbons, cause unexpected illnesses even at low-level exposures [14].

12.9 Other Sources of SBS Toxic Chemicals

There are numerous other sources of toxic chemicals released to the indoor environment which can account for or contribute to SBS. A few of these are given here.

12.9.1 Wood Smoke

It is estimated that 50% of the world's households use biomass fuel (most commonly wood) for indoor cooking purposes [32]. Though these households are found predominantly in developing nations, firewood smoke is not limited to them. Wood is used extensively in fireplaces and stoves for heating and esthetic purposes in the households of developed nations. When burned, wood emits particulates and VOCs that have respiratory toxicity. Wood smoke has been shown to be associated with the development of obstructive airways disease [32], and alone or in combination with other indoor air pollutants can contribute to SBS.

12.9.2 Textile Wall Materials

Building interiors decorated with textile and other soft fiber wall materials have been shown to induce mucosal irritation, allergic reaction, skin reaction, asthmatic response, and CNS symptoms associated with SBS. Such wall coverings typically release formaldehyde and other pollutants. They also adsorb and subsequently release other SBS-inducing chemicals [33].

12.9.3 Wood Dust

Indoor finishing and/or refinishing of wood components (floors, cabinets, counters, furniture, etc.) often liberates dust particles that induce respiratory symptoms, including asthma [34]. Mixed with other indoor air chemicals that are often associated with wood working, such as formaldehyde and aromatic hydrocarbons, wood dust is a powerful respiratory irritant.

12.9.4 Dioxins in Wood Preservatives

In the 1960s, paneling and other interior wood structures were treated with pentachlorophenol and γ -hexachlorohexane for preservation purposes. Those preservatives

contain trace quantities of polychlorinated dibenzo-*p*-dioxins and -furans which can volatilize into indoor air and impact the human immune system, particularly when the treated woods are being sanded and refinished, even many years after they were initially applied [35].

12.9.5 Waterproofing Applications

Fluorocarbon-based waterproofing agents are often applied to tiles in residential and commercial buildings. When spray is applied, these produce solvent vapors and aerosols that can cause acute respiratory injury [36, 37]. Fluorocarbon-based waterproofing materials for leather protection produce similar effects in many people [38].

12.9.6 Hot Asphalt Roof Applications

Hot asphalt roof applications generate mixtures of solvents and high-boiling organic compounds that can permeate into indoor air, particularly if air intakes are located on rooftops. These vapor mixtures, even when present in very low concentrations, can produce eye and upper respiratory tract irritation in building occupants [39].

12.9.7 Radon, Asbestos, and Tobacco Smoke

The sources just discussed primarily, but not exclusively, produce acute health effects. Some indoor pollutants that are not acutely associated with SBS produce only chronic effects. Three of the most notable of these are radon, asbestos, and tobacco smoke.

Radon is a carcinogen present in indoor air that is estimated by some studies to be responsible for about 1% of all lung cancers [40, 41]. Other studies, however, question whether it is radon alone or radon in combination with cigarette smoke exposure that is responsible for the cancers. Even those studies that question the effect of radon exposure as a cause of lung cancer, however, conclude that high-level radon exposure contributes to the lung cancer risk associated with exposure to tobacco smoke [42]. Nonsmoking residents of smoking households experience a synergistic, multiplicative effect on lung cancer rates even when radon rates are relatively low [43].

Chronic residential exposure to asbestos is known to be the cause of a specific lung cancer, mesothelioma [44]. Here, too, tobacco smoke exacerbates the carcinogenic effect. Asbestos workers who smoke are 90 times as likely to develop lung cancer as those who neither smoked nor worked with asbestos [45].

The studies just cited address the risk of developing lung cancer following exposure to radon, asbestos, and tobacco. Though estimating these risks is complicated by human exposures to other environmental pollutants, both indoors and outdoors [42, 44], these and other similar studies do definitively establish the enhanced effects of exposure to mixtures on the development of lung cancer and other cancers. This subject will be discussed further in Chapter 32.

12.10 Biological Causes of SBS

Though this book is devoted to chemically induced toxicity, the subject of SBS cannot be discussed without addressing biological causes of SBS. The presence of molds, dust mites, and animal allergens in residential and commercial buildings are known to produce adverse health effects in humans.

12.10.1 Molds

Damp buildings provide breeding grounds for molds, some of which are human pathogens. Molds found in building interiors include *Cladosporium*, *Alternaria*, *Aspergillus*, *Mucor*, *Rhizopus*, *Stachybotrys*, and *Chaetomium*. *Aspergillus*, *Stachybotrys*, and *Chaetomium* are of particular concern because they produce mycotoxins, toxic chemicals which are secondary metabolites produced by growing fungi. Many of these mycotoxins, aflatoxins produced by *Aspergillus flavus*, and satratoxin H and verrucarol, for example, are toxic to humans [46].

Mycotoxins are complex organic compounds, with molecular weights in the range of 450–500. They are nonvolatile at ambient temperatures, but become respirable when attached to airborne dust particles [47]. At least 350 different fungi are known to produce more than 400 individual toxins belonging to at least 20 different mycotoxin classes.

Human toxic effects attributed to fungi and their mycotoxins include mucosal irritation, fatigue, headache, and other neurotoxic effects, check tightness, onset of asthma, and other pulmonary disease. Aflatoxin is acutely lethal in high concentration exposures. It is also teratogenic and mutagenic. Chronic low-level exposures are carcinogenic, particularly to the liver. It is transformed in vivo into active components that bind to DNA and RNA. Aflatoxin has been associated with acute liver injury, estrogenic effects, renal effects, and prevention of embryo implantation [46, 47].

An excellent review of mold toxicity with 465 references can be found in Ref. [46].

12.10.2 Dust Mites

Dust mites are ubiquitous in indoor environments. They thrive in carpeting, bedding, upholstery, and other fabrics [48]. Dust mite exposure promotes IgE antibody production in susceptible individuals. Such people demonstrate symptoms that include itching and running eyes, allergic rhinitis, and asthma [49].

12.10.3 Animal Allergens

People who are allergic to dogs, cats, and other animals have their allergic reactions triggered by proteins associated with these animals. Cat allergies, for example, are triggered by glycoprotein Fed d1, found in the fur, pelt, saliva, serum, urine, mucous, salivary glands, and hair roots of the cat [50]. Animal allergens are not confined to the living quarters of animals. Cat and dog owners carry these allergens into other buildings on their

clothing and thus introduce these allergens to locations without pets, such as schools and other public buildings [51]. Such introductions of allergens give rise to SBS effects that are not easily traceable and necessitate the use of elaborate air filtration systems to remediate them.

12.11 Mixtures

SBS symptoms and illnesses can often be attributed to specific sources. Often, however, despite careful chemical and biological testing, the sources are not revealed. Industrial hygiene workups many times reveal chemical contaminant concentrations that are an order of magnitude or more below NOEL levels. People living or working in buildings with low levels of contamination may be affected during times they spend in these buildings and find relief when they are away from them. Remediation protocols are difficult to proscribe when the sources of the problems are unknown.

The author has investigated many SBS situations in homes, office buildings, and other commercial settings where symptoms could not be attributed to any one contaminant. In all these cases, where biological sources could be ruled out, the buildings were found to be contaminated with mixtures of hydrophilic and lipophilic chemicals [14]. Ascribing SBS to office buildings is often easier than to do so in homes. Homes typically contain few residents, and when only one person living there is symptomatic, factors other than SBS may be at hand. Office buildings typically have many people in them. When numbers of people become symptomatic, it usually implicates the building in which they work.

A recently identified SBS effect in homes is that of sulfides emitted from some drywall that was imported from China and extensively used in home construction and repairs in Florida, Louisiana, Virginia, and other states from 2004 to 2007. A “rotten egg” smell emitting from this drywall has produced respiratory and neurological symptoms in many of those exposed. This subject is more fully described in Chapter 17.

12.12 Investigating an SBS Incident

SBS incidents most commonly occur in new or newly renovated buildings that tend to be tightly sealed. In investigating an incident, one should first rule out biological causes. Mold can usually be eliminated as a cause when not physically evident on room surfaces and not smelled. Animal protein residues can be ruled out if dogs and cats are not present, and mites are generally not present in significant concentrations in new carpets and furnishings.

Most commonly, volatile chemicals are the causes of the symptoms that beset people in “sick” buildings. Formaldehyde is almost always present in new or remodeled buildings due to its off-gassing from carpets, plywood, particle board, and furniture made from composite materials. Occasionally isocyanates are the culprits, particularly when PU finishes are applied to wooden floors and cabinets. VOCs and

isocyanates can be readily tested for by collecting air samples and analyzing these via gas chromatography/mass spectrometry (GC/MS). Off-gassing of VOCs generally decreases with time. Abatement of symptoms as a function of time is a good indicator that VOCs are responsible for the symptoms.

There have been many instances when biological agents have been ruled out and all volatile chemicals have been shown to be present in concentrations below those believed to induce symptoms. In all such instances that have been reported in the literature, the symptoms have either been ascribed to ultrasensitive individuals or psychological responses on the part of those reporting the symptoms. Recent research has established that mixtures of lipophiles and hydrophiles at very low concentrations are responsible for inducing symptoms in such instances [14].

An example of an SBS workup reported in the literature for a new office building further illustrates the mixture effect [5]. A total of 154 employees who worked in the building during its first 2 weeks of occupancy experienced symptoms that included headache, fatigue, drowsiness, odor sensation, sore throat, nasal and sinus congestion, nausea, dizziness, sneezing, eye irritation, chest tightness, back pain, trouble sleeping, unusual taste, disorientation, chest congestion, aching joints, rapid heart-beat, skin irritation and itching, chest pains, unusual vaginal discharge, contact lens problems, tongue and lip numbness, bladder infections, and nosebleed. These symptoms ranged from 98 individuals with headache to 8 with nosebleed.

Chemical analysis of the air by GC/MS showed several VOCs, all present at concentrations far below ACGIH workplace TLVs. Table 12.7 shows the chemicals found, their concentrations, TLV and the K_{ow} values (octanol:water partition coefficients) for these. The data are those reported [5]. The K_{ow} values were added here.

Individually and collectively, assuming additive effects, one would not expect to observe the respiratory system, CNS, skin, and other symptoms reported by the employees in the subject building. The authors of the study concluded that although an outbreak of symptoms occurred, the causative agent(s) could not be identified. The K_{ow} values, however, show that three hydrophiles (formaldehyde, valeraldehyde,

Table 12.7 VOCs Found in the Air of a “Sick” Building, Their Concentrations in ppm [5], and the K_{ow} Values

Chemical	ppm	ACGIH TLV (ppm)	K_{ow}
Formaldehyde	0.02–0.04	1.0	0.35
1,1,1-Trichloroethane	<0.006	350	2.49
Styrene	<0.006	20	2.95
Ethyl benzene	<0.006	100	3.15
Toluene	0.012	50	2.73
TCE	<0.006	50	3.40
Valeraldehyde	<0.006	50	1.78
Xylenes	<0.006	100	3.15
2-Hexanone	<0.006	50	1.38
Benzene	<0.006	0.1	2.13

and 2-hexanone) and seven lipophiles (1,1,1-trichloroethane, styrene, ethyl benzene, toluene, TCE, xylenes, and benzene) were present in the building's air. As has been shown previously, the lipophiles facilitate the absorption, transport, and action of hydrophiles in parts of the body where the hydrophiles do not reach when exposure is to them alone [14]. It is concluded here that the actions of the mixture produced the unanticipated effects that were reported in the subject study.

The study just described is but one example of the lipophile:hydrophile mixture effect. I have investigated and reported on several SBS cases [14] and have not encountered any SBS case attributable to low-level chemical contamination that did not reveal the presence of mixtures of hydrophiles and lipophiles.

12.13 Summary

SBS describes the contamination of the indoor environment to the point where individuals living or working in these buildings become ill from inhaling the air. The contaminants can be in the form of chemical or biological agents. The chemical agents can arise from outgassing of carpets, structural wood, or furniture, as well as from paints, varnishes, adhesives, and other chemicals used. The exposures of people to interior air pollutants is almost always to mixtures of lipophilic and hydrophilic chemicals which act together to induce unexpected health effects.

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13 Industrial Exposure

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13.1 Introduction

There are approximately 80,000 industrial and commercial chemicals in use in the world today and many more are added each year. Essentially all of these exhibit toxicity individually to humans. Toxicological information for many, but not all, of these chemicals is available in the literature. This book is not written to explore the individual toxicities of chemicals. Rather, the intention here is to address mixtures. With so many chemicals in use, an extremely large number of mixtures are possible. Testing of all possible mixtures is impossible and most of the information available about the toxicities of mixtures arises from studies that track impacted workers.

In this chapter, examples of toxic effects of chemical mixtures on workers will be presented to demonstrate toxic impacts on those exposed on the job. In order to properly recognize mixture effects, one must have good information on the chemicals to which the individuals are exposed and one must also examine the toxicities of the individual chemicals to ascertain that the impact(s) on workers is due to a mixture effect and not simply that of a single chemical.

13.2 Single Chemical Toxicities

The toxicities of single chemicals are available from a number of databases and sources. Those listed here are not the exclusive resources, but they do provide toxicological information for most single chemicals.

1. Sittig's Handbook of Hazardous Chemicals and Carcinogens provides toxicological data on some 1300 specific industrial chemicals [1].
2. Sittig's Handbook of Pesticides and Agricultural Chemicals is a companion to Sittig's Handbook of Hazardous Chemicals and Carcinogens and provides toxicological information on nearly 800 pesticides and other agricultural chemicals [2].
3. Sax's Dangerous Properties of Industrial Materials [3].
4. PubMed, a service of the U.S. National Library of Medicine, includes over 16 million citations from MEDLINE and other life science journals back to the 1950s. PubMed contains abstracts of most papers cited and includes links to full text articles and other related resources. Resources may be accessed by subject matter, author, or journal [4].
5. TOXNET contains databases on toxicology, hazardous chemicals, environmental health, and toxic releases. TOXNET may be searched by subject matter, chemical name, or CAS number. Individual databases or all databases can be searched upon request [5]. The databases contained in TOXNET can all be accessed from one online source [5]. These databases include:
 - ChemIDplus—A dictionary of over 370,000 chemicals (names, synonyms, and structures). It includes links to the National Library of Medicine databases and resources.
 - HSDB—Hazardous Substances Data Bank. Comprehensive, peer-reviewed toxicology data for about 5000 chemicals.
 - TOXLINE—Contains references from the toxicology literature. Includes the peer-reviewed literature and government reports.
 - CCRIS—Chemical Carcinogenesis Research Information System contains carcinogenicity and mutagenicity information for over 8000 chemicals.
 - DART—Developmental and Reproductive Toxicology Database contains references to the developmental and reproductive toxicology literature.
 - GENETOX—Peer-reviewed genetic toxicology for over 3000 chemicals.
 - IRIS—Integrated Risk Information System contains hazard identification and dose-response assessments for over 500 chemicals.
 - ITER—International Toxicity Estimates for Risk contains information for over 600 chemicals from authoritative groups worldwide.
 - LactMed—Drugs and Lactation Database is a peer-reviewed and fully referenced database of drugs to which breastfeeding mothers may be exposed.
 - Multi-Database—Searches all factual chemical databases for toxicological information.
 - TRI—Toxics Release Inventory tracks annual environmental releases of over 600 toxic chemicals by U.S. facilities.

- Haz-Map—Contains information on hazardous chemicals and occupational diseases.
 - Household Products—Household Products Database contains health and safety information on products used in the household.
 - TOXMAP—Environmental health e-maps that explore data from EPA's Toxics Release Inventory and Superfund National Priorities List.
 - State of Maine, Department of Environmental Protection Chemicals of High Concern List—Lists more than 2000 toxic chemicals and their points of attack.
6. Scorecard is an online database that contains lists of 12 different adverse health effects. These include lists of chemicals that are (a) recognized and (b) suspected causative agents. Scorecard also provides links to comprehensive profiles for each chemical and summarizes the references that document that chemical's association with a health hazard [6]. The lists in scorecard include:
- Cancer
 - Developmental Toxicity
 - Reproductive Toxicity
 - Cardiovascular and Blood Toxicity
 - Endocrine Toxicity
 - Gastrointestinal or Liver Toxicity
 - Immunotoxicity
 - Kidney Toxicity
 - Musculoskeletal Toxicity
 - Neurotoxicity
 - Respiratory Toxicity
 - Skin or Sense Organ Toxicity.
7. NIOSH Pocket Guide to Chemical Hazards contains key toxicological information in abbreviated or tabular form for single chemicals or substance groupings (e.g., cyanides, fluorides, or manganese compounds) that are found in the work environment [7].

Additional information may be found in toxicology and molecular biology texts. Monographs on specific subjects, e.g., formaldehyde [8], provide compendia of toxicological information on specific chemicals.

13.3 Mixture Toxicities

Much of what is known about toxicology of chemical mixtures is the result of empirical observations and epidemiological studies carried out in the industrial workplace. The workplace provides an excellent setting to study toxic mixture effects. In the workplace, large numbers of individuals with varying genetic backgrounds and lifestyles are exposed to identical mixtures. The same illnesses developing among such diverse groups of people are indicative of unusual effects for which other variables, such as genetics, diet, and tobacco use, can be eliminated.

The following sections describe case study examples for which the effects of single chemicals have been ruled out. These studies represent only a fraction of those demonstrating the known effects of toxic mixture exposure. They are meant to illustrate the scope of hazards faced when humans are exposed to toxic chemical mixtures.

In almost all of the studies presented here (as well as in most others not reported here) the chemical mixtures that produced unanticipated toxic effects contained at

least one lipophile ($K_{ow} > 2.00$) and one hydrophile ($K_{ow} < 2.00$). The octanol:water partition coefficients (K_{ow}) are given in parentheses for each of the chemicals identified to point out the lipophilic and hydrophilic species.

13.4 Noise, Organic Solvents, and Hearing

Concurrent exposure to noise and mixed organic solvents is synergistically ototoxic, resulting in greater hearing loss to workers than if they were exposed to noise alone. In studies carried out on aviation and varnish manufacturing employees, it was shown that exposures to mixtures of lipophilic and hydrophilic compounds below TLVs concurrent with noise resulted in greater hearing loss in employees than anticipated [9, 10]. Paint and lacquer factory workers exposed to mixtures of xylenes (3.15) and ethyl acetate (0.73) were shown to have suffered greater hearing losses than workers with similar noise, but no solvent exposure [11].

13.5 Foundry Fumes and Cancer

Epidemiological studies of workers in the iron and steel foundry industry have shown 40% higher incidences of lung cancer in these workers than in the general population. They are exposed to foundry fumes containing complex mixtures of PAHs (lipophiles) and metal particulates (hydrophiles). An animal study showed that exposures to foundry fume mixtures produce preneoplastic lesions in test species [12].

13.6 Painting and CNS Effects

Adverse CNS effects (including neuropsychiatric disorders, mental symptoms, and neurobehavioral performance) are observed following exposures to solvent mixtures at levels well below accepted TLVs [13]. The neurotoxicity of *n*-hexane (3.90) is potentiated by 2-butanone (0.29), which itself exhibits little or no neurotoxicity to humans [14]. In one study, 100 automobile painters who had long-term exposure to car paint fumes composed of toluene (2.73), xylene (3.15), aliphatic hydrocarbons (3.90–5.50), ethanol (−0.31), isopropanol (0.05), butanol (0.88), ethyl acetate (0.73), butyl acetate (1.78), acetone (−0.17), MEK (0.29), MIBK (1.19), and pinene (4.83) at mean concentrations far below TLVs were shown to have impairments in psychological performances as well as personality changes compared to 102 control individuals [15].

Even short-term exposure to low levels of mixtures of lipophiles and hydrophiles can produce adverse neurological effects. Printers and spray painters so exposed to mixtures primarily containing *n*-hexane (3.90) and isopropanol (0.05) were found to have neurological symptoms, including polyneuropathy and diminished ankle reflexes [16].

13.7 Printers' CNS and Mucous Membrane Effects

A study of 762 printers exposed to low levels of *n*-hexane (3.90), isopropanol (0.05), and benzene (2.13) showed that these workers exhibited a number of neurological symptoms as well as mucous membrane irritation, effects not expected to be seen at low concentration exposure [17].

13.8 High Cancer Rates in Road Pavers and Roofers

PAHs are emitted into the air from a variety of industrial activities including highway paving and hot asphalt roof application. Exposures to PAHs from such activities result in increased levels of lung cancer [18, 19]. Concurrent exposure to PAHs (lipophiles) and heavy metals (hydrophiles) enhances the DNA damage due to PAHs alone. A study carried out on children living in a heavily polluted industrial locale showed that co-exposure to PAHs and lead increased the induction of cytogenetic effects in peripheral lymphocytes of children [20]. The air in and around smelters, refineries, and coal- and petroleum-fired electrical power plants frequently contains PAHs and heavy metals. Coal fly ash contains chromium, copper, manganese, nickel, lead, mercury, selenium, and zinc. Inhalation of such air presents risks of potentiated and synergistic toxic effects [21, 22].

13.9 Nail Salon Work and CNS Effects

Nail salon workers are exposed to low levels of a number of organic solvents including toluene (2.73), formaldehyde (0.35), ethyl acetate (0.73), *n*-butyl acetate (1.78), methacrylic acid (0.93), methyl methacrylate (1.38), and ethyl methacrylate (1.94). These exposures result in loss of cognitive efficiency, learning, memory, and neurosensory changes including olfaction, which among nail salon workers is below normal levels [23, 24].

13.10 Coke Oven Work and Smoking Synergism

Coke oven emissions expose workers to PAHs, VOCs, and heavy metals. Exposed workers suffer adverse liver effects [25], respiratory diseases [26], and cancer risks [27]. These effects are generally attributed to the PAHs and PAH-DNA adduct formation [28]. Such attributions, however, may only partially explain the observed health effects. For example, in a study carried out among 700 coke oven workers in China, the risk for developing COPD was significantly reduced for those coke oven workers who did not smoke cigarettes [26]. Even though cigarette smoke contains some of the same PAHs found in coke oven emissions, it contains other, unidentified, compounds which increase risk of COPD development. The authors of the adverse

liver effect on coke workers study also concluded that those adverse effects were caused by a mixture of chemicals, rather than by a single chemical species [25].

13.11 Incinerator Fly Ash Toxicity

Fly ash from municipal waste and industrial waste incinerators contains PCDDs, including TCDD, and PCDFs, which are lipophiles, and heavy metals, including chromium, copper, manganese, vanadium, and lead, which are hydrophiles [29–31]. These chemicals have multiple toxicities, and are known to impact the human liver, immune system, respiratory system, thyroid, male reproductive function, and CNS [32–34]. Several are human carcinogens [32, 35]. Enhanced toxic effects are observed for mixtures of some of these [21, 22, 36]. The mixtures of toxicants present in fly ash are complex and the mechanisms for their action on the human body are largely unknown. It is known that occupational exposure to fly ash from municipal and industrial waste incinerators increases the blood concentrations of PCDDs and PCDFs [29, 30]. It is also known that heavy metals absorbed from fly ash are translocated from the lungs where they first impact to other body organs where toxic effects are observed [31].

13.12 Naval Divers' Cancer Cluster

Cancer usually has long induction periods, generally 20 years or more, before the onset of lung cancer, e.g., in cigarette smokers. Naval commando divers, however, with prolonged skin, gastrointestinal tract, and respiratory system exposures to multiple carcinogenic agents experienced brief induction periods (less than 10 years) and had a cluster of hematolymphopoietic, CNS, gastrointestinal, and skin cancers. These effects were noted for Israeli commandos who regularly trained in a heavily polluted river contaminated with industrial, ship effluent and agricultural runoff contaminants [37]. The chemicals they were exposed to included numerous PAHs, long-chain branched hydrocarbons, chlorinated aromatic hydrocarbons (all lipophiles), benzene (2.13), toluene (2.73), xylene (3.15), styrene (2.95), phenols, alcohols, aldehydes, ketones, cadmium, chromium, cobalt, copper, mercury, nickel, lead, vanadium, zinc, organic and inorganic acids (all hydrophiles), trichlorophenol (3.70), di-(2-ethylhexyl)phthalate (7.60), methylene chloride (1.25), TCE (3.40), several radionuclides, and inorganic compounds. Clearly, it is difficult to ascribe any cancer to a particular chemical species. This study, however, points out the danger associated with exposure to mixtures of toxic chemicals by multiple body sites, as well as the propensity of chemical mixtures to induce multiple organ effects.

13.13 Industrial Solid Waste and Municipal Waste Leachate

Leachates from industrial solid waste (ISW) and municipal solid waste (MSW) sites contain complex mixtures of toxic chemicals. These include heavy metals (including

iron, nickel, zinc, manganese, chromium, cadmium, and lead) as well as numerous organic compounds (including aliphatic and aromatic hydrocarbons, PAHs, alcohols, esters, aldehydes, and pesticides). Specific compositions of leachates vary with pH, soil type, and specific chemicals contained in the sites. All ISW and MSW sites, however, leach toxic mixtures of chemicals. In one study, leachates from a polyfiber factory, an aeronautical plant, and a municipal sludge site were all shown to induce DNA damage in human peripheral blood lymphocytes. The authors of the study conclude that synergistic effects of the mixtures of chemicals in the leachates may be responsible for the DNA damage [38]. Similar cytotoxic effects were observed in studies where animals were exposed to ISW [39] and MSW [40] leachates. These studies underscore the dangers posed to ISW and MSW workers, as well as to people who are exposed to leachates that infiltrate drinking water.

13.14 Exposures of Workers to Aromatic Hydrocarbons

Exposures to aromatic hydrocarbons are known to produce a number of different effects in humans. Some aromatic hydrocarbon mixtures produce additive effects upon co-exposure, while others induce enhanced toxic effects.

In one study, a group of people who were exposed to a mixture of toluene (2.73) and mixed xylenes (3.15) was compared to a control group that was exposed to the individual solvents alone. Additive effects were noted when exposures were to the mixture versus the individual solvents. Hematology and serum biochemistry did not show any notable changes from exposure to single chemical versus the mixture [41].

An immunotoxicology study showed that co-exposure to a mixture of benzene (2.13) and toluene (2.73) resulted in the enhancement of the immunotoxic effects of benzene. The authors surmised that toluene competed with benzene for Phase I metabolizing enzymes, thereby causing benzene concentrations in the body to be higher than if benzene were present alone [42].

A study of petrochemical workers exposed to a mixture of benzene (2.13), toluene (2.73), and xylene (3.15), each below its TLV (and total VOCs below all three individual TLVs), produced hepatotoxic effects. No reason for the observed effect was offered, but it was concluded that exposure to low-level aromatic hydrocarbon mixtures can cause liver damage [43].

A study on the CNS depressing effects of toluene (2.73), ethylbenzene (3.15), and xylene (3.15), singly and in combinations, showed that CNS effects were increased when exposures were to mixtures. The enhanced effects observed were modest when employees were at rest, but were significantly higher when workers were exercising or performing manual work. The authors attributed the observed effects to pharmacokinetic interactions of the mixture elements [44].

The studies described above illustrate the difficulties in predicting the effects of mixtures, even when all components are chemically similar. In these studies, exposures to lipophilic mixtures of very similar compounds produced expected effects in one study and unanticipated effects in different body organs in the other studies.

These studies, as well as others describing the effects of lipophile/hydrophile mixtures, point out the need to limit exposures to aromatic hydrocarbons.

13.15 Polyhalogenated Aromatic Compounds

Several classes of polyhalogenated aromatic hydrocarbons are extremely toxic to multiple organs in humans. These include PCBs, PCDD, of which TCDD is the most toxic, and PCDF. All are ubiquitous in the environment, bioaccumulate in human adipose tissue, have long half-lives, and are toxic to multiple body organs in humans. PCBs are complete carcinogens and tumor promoters [45]. It is difficult to assess the cancer risk from PCB exposures because some combinations of PCB congeners (all lipophiles) act synergistically to increase the risk of cancer [46]. Further complicating the PCB picture is the fact that mixtures of PCBs and PCDDs have shown additive and synergistic effects as tumor promoters [47]. The mechanisms for these effects remain unknown.

These toxicities of polyhalogenated aromatic hydrocarbons will be elaborated upon in the chapters of Part III of this book.

13.16 Color Vision Impairment in Workers

Occupational exposure to mercury (0.08) and chemical solvents including styrene (2.95), tetrachloroethylene (3.40), *n*-hexane (3.90), toluene (2.73), and carbon disulfide (1.94) has been shown to impair color vision in exposed workers [48]. Color vision impairment was also observed for those exposed to solvent mixtures at levels below TLV values [49]. No explanation was offered by the authors for the observed mixture effect.

13.17 Irradiated Mail Sensitivity

Mail delivery to the U.S. Congress was suspended from October 2001 through January 2002, following the detection of anthrax spores in some congressional offices. When mail delivery resumed, all mail was irradiated with large doses of gamma radiation to eradicate anthrax spores in the mail. Shortly after resumption of mail delivery to Congress, many employees who handled irradiated mail experienced adverse health symptoms, including headaches, nosebleeds, nausea, rashes, and itching skin. NIOSH determined that the only air contaminants that could arise from irradiated mail were carbon monoxide (1.78), formaldehyde (0.35), ozone (−0.87), PAHs (all lipophiles), toluene (2.73), VOCs (mixtures of lipophiles and hydrophiles), and particulates. Sampling and testing for these showed that all of these substances were present at low levels or not detected. The NIOSH report concluded that the skin symptoms experienced by employees were because of damage to the paper resulting

from the radiation process. Other symptoms were attributed to odors which triggered symptoms in some individuals and/or employee stress [50]. The effects of low-level mixtures were not considered by the NIOSH report.

13.18 “Aerospace Syndrome”

In 1988, more than half of approximately 200 employees working with composite plastic materials in one building of an aircraft manufacturing company reported CNS, respiratory, heart, and gastrointestinal symptoms. The employee response was dubbed “aerospace syndrome.” Sampling of the air in that building showed the presence of phenol (1.46), formaldehyde (0.35), styrene (2.95), methylene chloride (1.25), methanol (0.77), C₉–C₁₂ alkanes and aromatics (3.0–4.0), particulates, and epoxy resins, all at concentrations well below their TLVs [51]. The author of the study concluded that, like the employees exposed to irradiated mail, the aerospace workers responded to psychosocial factors in the workplace.

13.19 Hospital Histology Technicians

Neurobehavioral symptoms, disturbed mental and neurological function, and respiratory symptoms were reported in histology technicians as a result of their exposure to formaldehyde (0.35), ethanol (–0.31), chloroform (1.97), toluene (2.73), and xylene (3.15). The symptoms observed could not be attributed to the individual chemicals at the low levels of exposure. This study illustrates the propensity of some lipophilic–hydrophilic mixtures to attack multiple organs, including ones not impacted by the individual toxins [52].

13.20 Persistent Toxic Chemical Compounds

Many toxic chemicals are in use worldwide. A great many of these are persistent in the environment. They have long half-lives and are passed up the food chain. Many are soluble in human adipose tissue and are slowly metabolized. The most persistent of these are [53]:

- PCBs
- DDT
- Dieldrin
- Toxaphene
- Mirex
- BaP (a PAH)
- HCB
- Dioxins (TCDD is the most toxic example)
- Furans

MeHg
Alkylated lead.

All of these persistent chemical compounds are toxic to multiple organs in humans. They are almost always present in mixtures rather than as single chemicals. With the number of chemicals involved and the usually complex mixtures they are found in, identifying specific mixture effects is difficult. Some mixture effects among these, however, have been identified. HCB (5.73) potentiates reduction of body and thymus weights caused by TCDD (6.80) and MeHg (0.08) acts synergistically with PCBs to disrupt the brain levels of dopamine that may influence neurological function and development [54].

13.21 Regional Impact Assessment

More than 30,000 different chemicals are produced or used in the Great Lakes region of the United States. This area contains 118 different hazardous waste sites that are contaminated with thousands of different chemicals. A study of this region has shown that human populations in it have elevated body burdens of persistent toxic chemical compounds. Those living in this region have been found to exhibit decreased gestational age, low birth weights, developmental effects in children, neurological defects in newborns, increased infertility, changes in sex ratios of children born, and thyroid hormone fluctuations [54].

Many of the observed Great Lakes region toxic effects are attributed to persistent toxic chemical compounds. TCDD is associated with human thyroid hormone fluctuation, male reproductive function, and neurological malfunction. HCB and MeHg are associated with human thyroid hormone fluctuation, female reproductive function, neurological, and neurodevelopmental problems. These effects, summarized in Table 13.1, illustrate the difficulty in attributing a particular toxic effect to a single chemical, particularly when one considers the potential impacts of thousands of other chemicals.

The authors of the study point out the need to consider “the potential for the joint toxic action of these substances in combinations in which they are typically found” [54].

Table 13.1 Toxic Effects of Persistent Toxic Chemical Compounds [54]

Effect	Chemical		
	TCDD	HCB	MeHg
Thyroid	X	X	X
Male Reproductive	X		
Female Reproductive		X	X
Neurological	X	X	X
Neurodevelopmental		X	X

13.22 Summary

On-the-job exposures offer insight into the toxic effects of chemical mixtures. Though many health effects can be attributed to exposures to single chemicals, others cannot be accounted for by single chemical exposures and are clearly related to exposures to mixtures. This is particularly the case when at least one component of the mixture is a lipophile and at least one other component of the mixture is a hydrophile. The studies referenced in this chapter point out the need to consider mixture exposures when people present with symptoms, rather than dismiss their complaints as being of psychological origin.

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14 Pesticides

Chapter Outline

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14.1 Introduction

Pesticides are toxic chemicals that are deliberately introduced into the environment for the sole purpose of killing living organisms. In the United States alone, hundreds of products containing more than 130 billion pounds of pesticides are applied annually [1]. The species pesticides target include animals, plants, bacteria, and fungi. All pesticides are toxic to humans and result in human exposures. They are applied with the anticipation that the quantities that humans may be expected to be exposed to will not prove to be hazardous because people are so much larger than the target species and hence not appreciably impacted by small amounts of these lethal poisons. As will be seen later, this has not turned out to be the case. Pesticides that are endocrine disruptors are indeed toxic to humans in low doses, as are mixtures of pesticides and the solvents commonly used to apply them.

Sources of human exposure to pesticides include agricultural application, commercial and home building disinfection, garden use, golf course and lawn use, manufacturing wastes, misuse, and handling accidents. Pesticide residues are present in foods and contaminated drinking water [1]. Many are volatile and result in exposure upon breathing. Pesticides are ubiquitous in the environment and contaminate virtually every source of drinking water on earth. In the United States, testing for pesticides found that they were present in every water source tested [2], in more than 70% of foods [3], and in the bodies of more than half of all adults and children [4].

14.2 Definitions

The term pesticide, as used here, is an all-encompassing one that includes all chemicals deliberately and legally used to prevent, destroy, repel, or mitigate any pest, that is, unwanted living species. Different subdivisions of pesticides, however, target different types of species. The following classifications list the chemical pesticide subdivisions and the species they target [1].

- Acaricides: Kill mites, ticks, and spiders that feed on plants and animals. Also called miticides.
- Algicides: Kill algae in ponds, lakes, canals, swimming pools, and industrial air-conditioners.
- Antifouling agents: Kill or prevent the attachment of organisms (such as barnacles) that attach to boat bottoms and other underwater surfaces.
- Avicides: Kill birds.
- Biocides: Kill micro-organisms.
- Biopesticides: Pesticides derived from natural materials (an example being pyrethrum which is an extract of dried chrysanthemum flowers).
- Defoliants: Cause leaves or other foliage to die and drop from trees and plants.
- Disinfectants: Kill micro-organisms on inanimate surfaces.
- Fumigants: Gases or fumes that kill insects, fungi, and other unwanted species in buildings or soil.
- Fungicides: Kill fungi, including blights, molds, mildews, and rusts.
- Growth regulators: Disrupt life processes of insects or plants.
- Herbicides: Kill weeds (unwanted plants), grasses, and other plants.
- Insecticides: Kill insects and arthropods.
- Molluscicides: Kill snails and slugs.
- Nematicides: Kill nematodes (microscopic, worm-like organisms that feed on plant roots).
- Ovicides: Kill eggs of mites and insects.
- Piscicides: Kill fish.
- Predacides: Kill vertebrate predators.
- Repellants: Repel insects and birds.
- Rodenticides: Kill mice, rats, and other rodents.
- Sanitizers: Kill micro-organisms on skin (generally added to soaps and cleaners used in medical settings and in home).
- Synergists: Enhance the killing power of active ingredients (nontoxic alone).

14.3 Human Toxicities of Pesticides

As noted earlier, all pesticides are toxic to humans. Different classes of pesticides, however, poison by different mechanisms. Organophosphates poison insects and animals primarily by phosphorylation of the acetylcholinesterase enzyme (AChE) at nerve endings, thus interfering with normal nerve impulse transmission. *N*-Methyl carbamates also poison by attacking the AChE and interfering with nerve transmissions. The other major class of pesticides, the organochlorines, are not cholinesterase

inhibitors, but they interfere with fluxes of cations across nerve cell membranes, increasing neuronal irritability, which causes convulsions and seizures [5].

The following is a representative profile list of the different chemical classes of pesticides, their modes of absorption, toxicities to humans, symptoms of exposure, pesticide uses, and exemplar compounds. The pesticide profiles presented here are for those pesticides that will be discussed later in this chapter. For a more extensive list of pesticide types, including brand names, and their toxicities, the reader is referred to the literature [1, 5].

Organophosphates

- | | |
|---|--|
| <ul style="list-style-type: none"> • Absorption • Human toxicity • Exposure symptoms | Inhalation, ingestion, dermal
AChE degradation
Weakness, loss of appetite, weight loss, headache, dizziness, shaking, nausea, stomach cramps, diarrhea, perspiration |
| <ul style="list-style-type: none"> • Pesticide uses • Exemplars | Insecticides, acaricides
Dichlorvos, chlorpyrifos, ethion, diazinon, dimethoate, acephate, malathion, azinphos-methyl, pirimiphos-methyl, terbufos, coumaphos, phosmet |

N-Methyl Carbamates

- | | |
|---|---|
| <ul style="list-style-type: none"> • Absorption • Human toxicity • Exposure symptoms | Inhalation, ingestion, dermal
AChE degradation
Weakness, headache, dizziness, shaking, nausea, stomach cramps, diarrhea, loss of appetite, perspiration |
| <ul style="list-style-type: none"> • Pesticide uses • Exemplars | Insecticides, acaricides
Aldicarb, propoxur, carbaryl, benomyl, propoxur, pyridostigmine bromide |

Organochlorines

- | | |
|---|--|
| <ul style="list-style-type: none"> • Absorption • Human toxicity • Exposure symptoms | Inhalation, ingestion, dermal
Nervous system disruption, mainly of the brain
Headache, dizziness, shaking, disorientation, weakness, nervousness |
| <ul style="list-style-type: none"> • Pesticide Uses • Exemplars | Insecticides and acaricides
Lindane, chlordane, dieldrin, mirex, DDT, toxaphene, chlordecone, endosulfan |

Chlorophenoxy Compounds

- | | |
|--|--|
| <ul style="list-style-type: none"> • Absorption • Human toxicity | Inhalation, ingestion, dermal
Eye, skin, lung, stomach, and intestinal mucous membrane lining irritant; injures liver, kidneys, and CNS |
| <ul style="list-style-type: none"> • Exposure symptoms • Pesticide uses • Exemplars | Diarrhea, muscle twitching, burning in stomach
Herbicides
2,4-D, 2,4,5-T, dicamba, mecoprop, 2-(2-methyl-4-chlorophenoxy)propionic acid (MCPP) |

Pyrethrins and Pyrethroids

- | | |
|--|-----------------------|
| <ul style="list-style-type: none"> • Absorption | Inhalation, ingestion |
|--|-----------------------|

(Continued)

- Human toxicity Low human toxicities by themselves
- Exposure symptoms Irritating to mouth, nose, throat
- Pesticide uses Insecticides and acaricides
- Exemplars Pyrethrin, dimethrin, fenvalerate, permethrin, bifenthrin

Triazines

- Absorption Inhalation, dermal
- Human toxicity Low human toxicities by themselves
- Exposure symptoms Moderately irritating to eyes, skin, respiratory system
- Pesticide uses Herbicides
- Exemplars Atrazine, cyanazine

Paraquat and Diquat

- Absorption Inhalation, ingestion, dermal, ocular
- Human toxicity Skin, eyes, cornea, liver, kidneys, respiratory system, gastrointestinal tract
- Exposure symptoms Burning pain, nausea, vomiting, diarrhea, injures skin and nails
- Pesticide uses Herbicides

Diethyltoluamide (DEET)

- Absorption Ingestion, dermal
- Human toxicity Skin
- Exposure symptoms Contact dermatitis, exacerbates pre-existing skin disease
- Pesticide uses Insect repellent

Acetamides

- Absorption Ingestion, dermal
- Human toxicity Low human toxicities by themselves
- Exposure symptoms Irritating to eyes and skin
- Pesticide uses Herbicides
- Exemplars Metolachlor, allidochlor

Analides

- Absorption Inhalation, dermal
- Human toxicity Dermal irritant and sensitizer
- Exposure symptoms Irritating to eyes, skin, and respiratory system
- Pesticide uses Herbicides
- Exemplars Alachlor, propachlor, propanil

14.4 Toxicity of Pesticide Mixtures

Pesticides are often applied in mixtures. Mixtures of herbicides, fungicides, and pesticides are applied to corn, cotton, lettuce, and fruit crops [6]. As a result, pesticides are widely present in the environment as mixtures. This point is underscored by the finding that more than 50% of all streams tested in the United States contained five or more pesticides [2].

The toxic effects of some pesticide mixtures are additive, particularly when their toxic mechanisms are identical. The additive effects of the organophosphates, such as chlorpyrifos and diazinon, were demonstrated in one study [7]. Another study

found *s*-triazine herbicides, such as atrazine and cyanazine, to show additive toxic effects [8]. Not all mixtures of similar pesticides produce additive effects, however. In one study, mixture of five organophosphate pesticides (chlorpyrifos, diazinon, dimethoate, acephate, and malathion) was shown to produce greater than additive effects when administered to laboratory animals [9]. Another paper discusses non-simple additive effects of pyrethroid mixtures. Despite their chemical structure similarities, pyrethroids act on multiple sites, and mixtures of these produce different toxic effects [10].

Exposures to mixtures of different classes of pesticides produce effects that are often difficult to anticipate. A large number of such mixtures produce synergistic effects. Organophosphate insecticides enhance pyrethroid toxicity when applied together [11]. Triazine herbicides potentiate the cholinesterase inhibiting property of organophosphates. For example, atrazine (a triazine herbicide) does not by itself reduce cholinesterase activity. Mixed with chlorpyrifos (an organophosphate), it significantly reduces AChE activity compared with chlorpyrifos alone [12]. Similar results were obtained with a mixture of cyanazine (also a triazine herbicide) and chlorpyrifos. It is hypothesized that the herbicides affect CYP450 enzymes that metabolize organophosphates [13]. In another study, diazinon (an organophosphate) and benomyl (a carbamate), which individually did not exhibit genotoxicity, were found to be genotoxic when administered together [14].

Amphibian endocrine disruption is of special interest to humans. The estrogen found in the painted turtle is identical to that found circulating in the human bloodstream and the endocrine disruptors that threaten wildlife populations have also been shown to be jeopardizing human reproduction [15]. Accordingly, animal studies on endocrine disrupting properties of toxic chemicals are relevant to understanding human responses to these chemicals. Pesticide mixtures have been shown to be powerful endocrine disruptors in numerous other animal studies [16]. Illustrative examples are as follows.

Hayes et al. [16] examined the effects of a realistic mixture of nine pesticides applied to cornfields in Nebraska. In the study, the effects of a mixture containing four herbicides (atrazine, metolachlor, alachlor, and nicosulfuron), three insecticides (cyfluthrin, cyhalothrin, and tebupirimphos), and two fungicides (metalaxyl and propiconazole) were compared to those of the nine individual components. All chemicals were present at very low levels (0.1 ppb) similar to those found in the environment. The effects on larval growth and development and immune function in leopard frogs were examined. The results show that although some of the pesticides individually inhibited endocrine disruption (larval growth and development and delayed gonadal development), the mixture had much greater effects. Exposure to the mixture retarded larval growth and development, delayed metamorphosis, reduced animal size at metamorphosis, and resulted in underdevelopment of gonads. The mixture of nine pesticides also induced damage to the thymus, resulting in immunosuppression and contraction of flavobacterial meningitis. The authors concluded that examining only single pesticides at high concentrations for toxicity may lead to "gross underestimations" of pesticide toxicities.

The similarities between human and wildlife hormones were also demonstrated in another study. The American alligator and human estrogen receptors were incubated

with [^3H]17-beta-estradiol (ED) in the presence of chlordane (which has no estrogenic activity), dieldrin, and toxaphene (which have very weak estrogenic activity). A combination of the three pesticides inhibited the binding of estradiol by 20–40%. A mixture of dieldrin with alachlor (which also has weak estrogenic activity) also resulted in a greater than predicted estradiol inhibition [17].

The chlorinated pesticides, DDT and chlordecone, are known to generate deleterious reproductive effects. In a bioassay of these and other chlorinated pesticides on cultured human breast estrogen-sensitive MCF7 cells, it was shown that dieldrin, toxaphene, and endosulfan have estrogenic properties comparable to those of DDT and chlordecone. When tested together, the mixture of the three pesticides induced estrogenic responses at lower concentrations than those required when the compounds were tested individually [18].

The urine of randomly selected men in agricultural environments of reproductive age was analyzed for parent compounds and metabolites of pesticides and compared with sperm concentration. The results showed that those exposed to mixtures of organophosphates and pyrethroids had lower sperm concentrations and that sperm concentration was related to the exposure levels of the two pesticide categories [19].

Pesticide mixture exposure has been linked to parental infertility, SAB, preterm delivery, and congenital abnormalities. Mouse embryos were exposed to mixtures of six herbicides (2,4-D, pendimethalin, atrazine, dicamba, metolachlor, and mecoprop), three insecticides (chlorpyrifos, terbufos, and permethrin), two fungicides (chlorothalonil and mancozeb), and a fertilizer (ammonium nitrate). The mixtures simulated exposures encountered by handling pesticides, inhaling airborne matter, or ingesting contaminated groundwater. Incubating embryos with mixtures increased apoptosis in exposed embryos, and reduced development to blastocyst and mean cell number per embryo. The authors concluded that the data demonstrate that injury from pesticide mixture exposure can occur early in development and at exposure concentrations generally not believed to affect humans [20].

In a study using a human neuroblastoma cell line, mixtures of three different organophosphates (azinphos-methyl, diazinon, and dimethoate) and mixtures of an organic phosphate (pirimiphos-methyl) and a benzimidazole fungicide (benomyl) showed greater toxicity toward protein synthesis than the individual pesticides [21]. The authors of the study concluded that it is not feasible to predict the toxicities of pesticide mixtures on the basis of the toxicities of the single components.

Approximately 30,000 veterans of the first Gulf War in 1991 have reported neurological, dermal, respiratory, musculoskeletal, and gastrointestinal symptoms of unknown etiology, commonly referred to as Gulf War syndrome. The causes remain unknown, but one hypothesis offered suggests that the symptoms may be attributable to pesticides that were used in the field. Soldiers were given a mixture of DEET (an aromatic amide insect repellent), permethrin (a pyrethroid insecticide), and pyridostigmine bromide (PB, a quaternary dimethyl carbamate to protect against potential nerve gas attack). In laboratory testing on hens, binary mixtures of any two of these three compounds produced greater neurotoxicity (including locomotor dysfunctions—reluctance to walk, impaired flying ability, and tremors) than that caused by the individual species. Neurotoxicity was further enhanced by concurrent

administration of all three compounds. At the dosages administered, all three compounds exhibited minimal neurotoxicity [22].

Similar results were observed when laboratory rats were treated with mixtures of the same pesticides. Mixtures of DEET and promethrin, DEET and PB, and promethrin or all three and PB led to locomotor and sensorimotor dysfunctions as well as significant decreases in AChE activities in the brains of laboratory animals treated with these mixtures. Individually, the three pesticides did not affect motor functions or have any inhibitory effect on plasma or brain cholinesterase activities [23].

14.5 Inert Ingredients in Pesticides

Pesticides that are placed into the stream of commerce for agricultural and home use are almost always mixtures of active ingredients and other ingredients put into the formulation to increase solubility, increase absorption by targeted species, adjust pH, alter viscosity and flow properties, and produce homogeneity. The other materials, which typically make up greater than 50% of most pesticide formulations and more than 90% of many, include solvents, surfactants, synergists, colorants, preservatives, and antifoaming agents. These other materials, which often are not identified on package labeling and product literature, are also referred to as inert ingredients.

Inert ingredients are presumed to have no physical, chemical, or biological activity, but this is not always the case. Pesticide testing, required to register pesticides, is mostly performed with the active ingredient alone, not the complete formulation. Many of the so-called inert ingredients, of which there are currently about 3000 in use [24], are themselves toxic. For example, a commercial herbicide that contains glufosinate ammonium (GLA) as its active component and an anionic surfactant, sodium polyoxyethylene alkylether sulfate (AES), decreases blood pressure and alters the heart rates of rats. GLA alone does not affect either parameter, whereas AES alone does [25]. Xylene, used as a solvent in many pesticides, is a known human neurotoxin [26].

Numerous studies demonstrate that inert ingredients enhance the toxicities of the active ingredients in pesticide formulations [27]. Examples of such effects are as follows.

Commercial formulations of pyrethrins usually contain piperonyl butoxide (PO). PO is a well-known synergist that inhibits the metabolic degradation of pyrethrins and thereby intensifies the effects of the active ingredients of pyrethrins [28, 29].

Surfactants and solvents are added to commercial pesticides to increase adsorption by targeted species. These chemicals also enhance the adsorption through mammalian skin. In a laboratory animal experiment, dermal penetration of atrazine, alachlor, and trifluralin was significantly lower for the pesticides alone than when contained in commercial versions of all three. It was also shown that the solvents contained in the commercial trifluralin enhanced the dermal penetration of the other two commercial formulas when the pesticides were mixed together [30]. Pesticides are often applied in mixtures. This study shows that such mixing can have important implications for the health of those who come in contact with such mixtures.

In another dermal penetration study, it was shown that the absorption of the insecticide carbaryl was enhanced by the solvent acetone and the surfactant sodium lauryl sulfate. The synergist PO significantly increased the absorption of carbaryl when added to the acetone–carbaryl mixture [31]. This study points out both the enhanced absorption of pesticide by individual inert additives as well as the further enhanced mixture effect.

Lindane absorption through human skin was studied *in vivo* and *in vitro*. Both studies showed that commercially formulated lindane products, which contained white spirits (a lipophile) as a solvent, were significantly higher than from acetone (a hydrophile) solution [32, 33].

Bifenthrin is the active ingredient in an insecticide sold for home use. Bifenthrin alone is not toxic to rodent nerve cells at 10^{-3} M concentration. A household-use product containing bifenthrin, however, was shown to be neurotoxic at concentrations of 10^{-6} and 10^{-7} M [34]. The authors concluded that the enhanced toxicity of bifenthrin is attributable to the “inert” additives in the commercial product.

The “inert” ingredients formulated into herbicides containing 2,4-D were shown to multiply the inhibition of mitochondrial oxidative activity of 2,4-D by as much as 136 times relative to the herbicides alone [35]. Similar results were found for formulations containing 2,4,5-T [36].

The herbicide glyphosate alone does not show any effect on mitochondrial oxidative phosphorylation. When formulated into a commercial pesticide, it causes a significant reduction in the activity of rat liver mitochondrial respiratory complexes [37]. Glyphosate-containing products also contain surfactants, antifoaming agents, colorants, biocides, and inorganic ions for pH adjustment [38]. No mechanism for the enhanced toxicities of formulated glyphosates has been advanced, though it is thought that the surfactants facilitate the absorption of the active ingredient and hence its toxicity.

Atrazine, one of the most widely used herbicides in the world, is not genotoxic and does not induce apoptotic or necrosis in human lymphocytes. A commercial herbicide containing atrazine, however, was shown to damage human lymphocyte DNA *in vitro*, as did the adjuvant (additive) mixture alone contained in the product [39]. The authors of the study attributed the toxicity to the adjuvant mixture contained in the commercial product.

The inert components of pesticides can also contribute to their absorption by humans by facilitating the transport of pesticides through protective clothing. A commercial formula containing iso-octyl ester of 2,4-D was shown to penetrate through neoprene and nitrile gloves. The penetration was ascribed to a cosolvent effect involving the inert components of the formulation [40].

14.6 Low-Level Pesticide Poisonings

The toxicological properties of individual pesticides are well known [41]. The effects of poisoning by low levels of pesticides and pesticide mixtures have not been well documented. These effects are the subject of this section. The octanol:water

partition coefficients (K_{ow}) are given for each of the chemicals in this section, so as to demonstrate the effects of exposures to mixtures of lipophiles and hydrophiles.

Exposures to low levels of pesticides are those that occur when toxic effects are observed following inhalation, ingestion, or dermal absorption of concentrations not known to be toxic. An example is the exposure to a commercial formulation of a bifenthrin (8.15)-containing insecticide that was shown to be neurotoxic at levels three to four orders of magnitude lower than the NOEL for bifenthrin alone [34]. Other chemicals contained in the commercial formula include a surfactant, heavy petroleum naphtha (5.0–6.5), and aromatic petroleum distillate (5.0–7.0).

Chronic low-level exposures to pesticides can lead to permanent neurological impairment. A study of banana workers illustrates this point. The psychomotor and visuomotor skills of 81 banana workers who had previously received nonhospitalization medical attention for mild exposures to organophosphate or carbamate pesticides were diminished relative to a control group of 130 banana workers who had never sought medical attention for pesticide exposure. The diminished effects were observed an average of 27 months after the reported exposures [42].

The toxic effects of low-level pesticide exposure can follow single or chronic exposures. The following examples illustrate this.

A mystery illness that affected 17 casino workers following fumigation of the premises with a pesticide mixture that contained the carbamate propoxur (1.52), the organophosphate coumaphos (4.13), 1,1,1-trichloroethane (2.49), methylene chloride (1.25), xylene (3.15), and acetone (−0.24) was reported. Industrial hygiene evaluation revealed only trace quantities of the chemicals noted, yet pesticide poisoning symptoms were observed in the employees [43]. No explanation for the effects was offered by the investigators.

Low levels of an applied herbicide–pesticide–solvent mixture were drawn into the uptake air of a commercial building following the application of a pesticide mixture to the lawn in front of that building. Several employees immediately reported CNS and respiratory symptoms, with one sustaining a permanent respiratory injury. The pesticide mixture applied to the lawn was composed of 2,4-D (2.82), MCPP (2.48), and dicamba (2.21). The mixture also contained solvent naphtha (a mixture of aliphatic solvents, K_{ow} = 3.5–5.0) with 14% naphthalene (2.48) and dinitroaniline (3.30). The concentrations of all pesticides and solvents were far below the TLVs both outside and inside the building. The toxic effects observed were ascribed to the mixture of lipophilic and hydrophilic pesticides [44].

Neurobehavioral deficits in those exposed to low levels of pesticides were observed by administering neurobehavioral tests to a group of migrant Hispanic farm workers who were exposed to low levels of azinphos-methyl (2.75), phosmet (2.78) and malathion (2.36), and a control group of non-agricultural Hispanic immigrant population. The farm workers were shown to have been exposed to low levels of pesticides in the fields and via dust in their homes. Significant neurological deficits were observed in the agricultural workers exposed to low levels of pesticides relative to the control group [45]. In another study, preschool-aged children living in agricultural communities in close proximity to fields where pesticides were applied had

impaired neurobehavioral performances similar to those observed in adults exposed to low levels of organophosphate pesticides [46].

Agricultural workers often experience long-term low-level pesticide exposures. In a study of 175 farm workers so exposed, it was found that chronic exposure (over many years) to low levels of pesticides produced neurological impairments similar to those observed in acute organophosphate pesticide poisonings [47].

Chronic peripheral nervous system effects have been reported in farmers who applied the organophosphate pesticides methyl parathion (2.86), azinphos-methyl (2.75), and tetraethylpyrophosphate (0.45) in xylene (3.15) solutions and were exposed to levels below those known to produce acute or subacute symptoms [48]. Similar effects were described in another study of low-level exposure to organophosphate pesticides [49]. In both cases, it is hypothesized that the lipophilic solvent (xylene) facilitated the absorption of greater than expected quantities of the more hydrophilic pesticides [44].

Neurological effects are not the only ones that result from low-level pesticide exposure. Endocrine and immunological effects have also been reported.

A large number of ubiquitous environmental pollutants are very toxic to the hypothalamic–pituitary–thyroid (HPT) axis when administered at high (greater than environmental) levels. To study low-level effects on the HPT axis, laboratory animals were administered a mixture of 16 organochlorine pesticides and other chlorinated hydrocarbons and heavy metals, all at levels similar to those found environmentally, so as to simulate environmental exposure. The chemicals included DDT (6.91), HCB (5.73), TCDD (6.80), PCBs (6.29), methoxychlor (5.08), endosulfan (3.83), heptachlor (6.10), hexachlorocyclohexane (3.80), dieldrin (5.40), aldrin (6.50), mirex (7.18), several chlorinated benzenes (2.84–3.44), cadmium (−1.65), and lead (1.35). Effects were measured by monitoring thyroid activity. The study found that this mixture of environmental pollutants was toxic and can alter HPT physiology in sexually mature males [50].

Human natural killer (NK) lymphocytes are vital to immune system defense against viral infection. They are also crucial in protecting against primary tumor formation. *In vitro* exposures to low levels of two organotin pesticides, tributyltin (4.76) and triphenyltin (4.19), and two carbamate pesticides, maneb (0.62) and ziram (1.23), produced significant loss of cytotoxic function of NK cells after 6 days of exposure. The toxicities of the pesticides also increased very significantly with exposure durations [51]. It should be noted that exposure to ziram can come from other sources. It is used as an additive in rubber products such as latex gloves.

14.7 Summary

Pesticide mixtures have been found to exhibit greater than additive effects when administered together. These enhanced effects may be due to the actions of the pesticides themselves, the presence of so-called inert ingredients in their formulations, synergistic interaction with other environmental pollutants, or combinations of these.

All the low-level pesticide effects discussed earlier ensued following exposures to mixtures that contained lipophilic and hydrophilic components. This is consistent

with the manner in which pesticides are formulated and applied; that is, as mixtures of products, each of which is composed of lipophilic and hydrophilic components. An exhaustive search of the literature did not produce a single example of low-level pesticide activity of individual pesticides at concentrations at which the pesticide mixtures exhibited toxicity.

As was seen, solvents and/or surfactants contained in one pesticide formulation can activate a low-level response in a second pesticide present in a mixture. Similar activation effects may be induced by the action of non-pesticide toxic chemicals present in the environment with pesticides.

The studies reviewed in this chapter clearly demonstrate that accurate evaluations of pesticide toxicity cannot be made by studying the toxicities of individual pesticides isolated from additive chemicals in their formulations and from other chemicals with which they may reasonably be expected to mix after application.

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15 Alcohol and Tobacco: Recreational Toxins

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15.1 Introduction

This chapter addresses the toxic effects of mixtures of two recreational toxins, ethanol and tobacco. These are the most abused chemicals in the world and both are used recreationally worldwide. There are many other recreational drugs in use. These include, e.g., marijuana, cocaine, heroin, and methamphetamines. These other recreational drugs will not be addressed here, except where they are components of xenobiotic mixtures that produce unanticipated toxic effects. At this time there is

a substantial volume of information that describes unanticipated toxic effects of ethanol and tobacco when used in conjunction with other toxicants. That information is the subject of this chapter.

It should be noted that organic solvents are deliberately inhaled (a practice known as huffing) by some for their intoxicating effects. The toxic symptoms which follow huffing are substantially identical with those observed following accidental inhalation. Inhalation toxicity is addressed in several parts of this book and will not be covered here.

15.2 Ethanol: Introduction

Humans have been deliberately imbibing alcoholic beverages since the Stone Age (*ca.* 10,000 B.C.). Alcoholic beverages were consumed by the Chinese *ca.* 7000 B.C., by the Egyptians *ca.* 4000 B.C., by the Babylonians *ca.* 2700 B.C., and by the Greeks *ca.* 2000 B.C. The Hebrews were introduced to wine during their captivity in Egypt and passed it down to Christianity. Throughout history, alcoholic beverages have been part of the religious rites of man [1]. As a result, the use of alcohol is deeply ingrained into most of the cultures of the world. It is consumed by vast numbers of people for religious and recreational purposes.

Ethanol is a toxic chemical with a dose–response relationship between quantity consumed and toxicity. It exhibits toxicity to the following parts of the human body:

- Digestive tract
- Liver
- Cardiovascular system
- Brain
- Reproductive system
- Fetal development
- Excretory system
- Respiratory system.

This chapter will not address the individual toxic effects of ethanol. Rather, in keeping with the theme of this book, the effects of mixtures containing ethanol will be examined. It will be seen that ethanol exacerbates the effects of other toxicants when co-consumed with these and induces effects not associated with exposures to the other individual toxicants, nor with ethanol alone. It is not implied here that all consumption of ethanol is hazardous to one's health. Indeed, positive effects of moderate ethanol consumption, including reduced coronary disease, have been reported in the literature [2]. With notable exceptions (e.g., use by alcoholics and diabetics), it is the excessive imbibing of ethanol that is responsible for its toxic effects.

15.3 Mechanisms of Ethanol Mixture Toxicity

Ethanol and other xenobiotics are metabolized in the same manner. Cytochrome P450 2E1 (CYP2E1) is the key enzyme in ethanol metabolism. CYP2E1 is inducible by chronic ethanol consumption. Its activity in the liver is three- to fivefold greater

in chronic abusers and accounts for the tolerance of ethanol in chronic abusers. This metabolic tolerance persists for several days following cessation of ethanol consumption. CYP2E1 also oxidizes other toxic chemicals including benzene, TCE, carbon tetrachloride, other organic solvents, and nitrosamines (present in food and tobacco smoke) to toxic metabolites and carcinogens. Accordingly, heavy consumption of ethanol which induces CYP2E1 increases the individual susceptibility of those who are exposed to these other xenobiotics even when adsorption of these occurs subsequent to ethanol ingestion via on-the-job and/or in the home exposures to chemicals, polluted air, contaminated water, dietary intake, and other sources [3–5].

Another mechanism of ethanol toxicity involves OS. Ethanol-induced liver disease is associated with significant OS as well as with increased levels of iron, which is also known to initiate OS in the liver. The combined OS induced by ethanol and iron greatly increases, resulting in lipid peroxidation and the production of aldehydes such as 4-hydroxy-2-nonenal, compounds which have been shown to cause mutations in the p53 gene. The greatly enhanced OS resulting from the combined effects of ethanol and iron is believed to be responsible for increased incidences of hepatocellular carcinomas (HCCs) in individuals who have high liver iron levels and consume ethanol [6].

15.4 Effect of Ethanol on Nutrients and Drugs

The following are examples of the effect of ethanol on nutritional components and drugs that are caused by metabolic induction.

Retinol is metabolized by the same enzymes that oxidize ethanol. As a result, prolonged use of ethanol, which induces those degradative enzymes, results in the breakdown of retinol to toxic metabolites. Ethanol also interferes with the conversion of beta-carotene, a precursor to vitamin A, to retinol. Thus ethanol both promotes the deficiency of vitamin A and enhances its toxicity and that of beta-carotene [7].

Acetaminophen is a widely used analgesic. Pretreatment with APAP followed by ethanol intake increases the metabolism of acetaminophen and thereby its toxicity. Binge drinking of ethanol increases the hepatotoxicity of acetaminophen [8]. Caffeine also activates the metabolism of acetaminophen and it, too, increases the hepatotoxicity of acetaminophen. The combination of ethanol and caffeine significantly increases the liver toxicity of acetaminophen [9].

Caffeine causes intracellular calcium levels to increase and thereby increases apoptosis induction. Ethanol promotes higher calcium levels and higher apoptotic rates than caffeine. When caffeine and ethanol are combined, however, increased calcium levels and apoptosis are markedly elevated, indicating that the apoptotic effect of ethanol is potentiated when it is mixed with caffeine [10].

15.5 Toxicity of Ethanol Mixtures with Other Chemicals

Combined exposure to ethanol and numerous other chemicals produces enhanced toxic effects. The following studies are examples of such interactive effects.

Benzene's toxicity is attributed to its metabolites. These can be accurately measured in urinary output. In a study to measure the effect of alcohol on benzene metabolic output, laboratory animals were treated with ethanol and exposed to benzene vapors. The urinary output of benzene metabolites was significantly lower in the animals treated with both ethanol and benzene than in control animals exposed to benzene alone. The study shows that the reduced output of benzene metabolites results from ethanol acting to retain these toxins in the body. The authors conclude that chronic ethanol ingestion exacerbates benzene myelotoxicity [11].

The human CNS toxicity of inhaled *m*-xylene is enhanced by ethanol ingestion. This effect markedly and nonlinearly increases with ethanol dose and is attributed to the fact that both *m*-xylene and ethanol are metabolized by the CYP2E1 enzyme and that ethanol is preferentially metabolized, resulting in higher residual levels of *m*-xylene [12]. The action of ethanol on *m*-xylene CNS toxicity points out the need to consider ethanol consumption when establishing safe exposure levels for VOCs.

Ethanol potentiates the toxicity of carbon tetrachloride. This phenomenon is exemplified by a report in the literature of human exposure to carbon tetrachloride. In two separate instances, acute liver and kidney poisoning ensued following exposure to carbon tetrachloride vapors from a discharged fire extinguisher. In both cases, other workers exposed to the same vapors for the same period of time showed no toxic signs or symptoms. Upon investigation, it was determined that the two injured individuals were chronic ethanol users, with daily consumptions of 120 and 250 g of ethanol per day, respectively. Each of their nonaffected coworkers consumed less than 50 g of ethanol per day [13].

Exposure to 2,2-dichloro-1,1,1-trifluoroethane (HCFC-123) produces reversible liver lesions in laboratory animals. When exposure to HCFC-123 was coupled with ethanol ingestion, liver toxicity was markedly increased. The increase, due to CYP2E1 induction, greatly enhanced the metabolism of HCFC-123 to compounds that are toxic to the liver [14]. HCFC-123 is a widely used substitute for banned ozone-depleting chlorofluorocarbons. This study strongly suggests that exposure to HCFC-123 can lead to toxic end points in individuals who chronically consume ethanol.

As was discussed in Section 13.3 concurrent exposure to noise and some organic solvents and solvent mixtures is ototoxic. Styrene is an example of an ototoxic compound, with exposures to it causing permanent hearing threshold shifts and outer hair cell damage. Ethanol alone does not affect auditory sensitivity, yet combined with styrene it induces hearing and outer hair cell losses in test animals that are greater than those caused by styrene alone. The potentiation of the ototoxicity of styrene by ethanol is ascribed to the altering of styrene metabolism by ethanol [15].

Hydrogen peroxide (H_2O_2) is cytotoxic. In one study, treatment of PC12 cells with H_2O_2 resulted in nuclear damage, decrease in the mitochondrial transmembrane potential, increase in ROS formation, and depletion of GSH. When H_2O_2 treatment was combined with ethanol, synergistic effects were observed. Relative to H_2O_2 alone, the combination of H_2O_2 and ethanol resulted in increased cell death as a function of exposure time. Nuclear damage, change in mitochondrial membrane permeability and ROS were all increased, and GSH levels in cells were decreased. The

authors of the study opine that ethanol enhances H_2O_2 viability loss by promoting mitochondrial membrane permeability change, which is associated with increased ROS formation and GSH depletion [16].

Heavy metals target the CNS. The toxic CNS effects of heavy metals are enhanced by consumption of ethanol [17]. In one study, laboratory animals were treated with lead alone and with a combination of lead and ethanol. In this study, ethanol enhanced the toxicity of lead in the brain via decreased cellular energy reserves (ATP levels). Co-exposure to lead and ethanol caused a significant decline in the rate of mitochondrial respiration compared to that induced by lead alone [18].

Dibutyltin dichloride (DBTC) is a widespread environmental pollutant that exhibits developmental toxicity in animals [19] and immunotoxic effects in human cells in vitro [20]. No studies were found in the literature that compared the developmental and immunotoxic effects of DBTC alone to a mixture of DBTC and ethanol. One study, however, found that ethanol coadministered with DBTC increased the toxicity of DBTC in the liver and pancreas of laboratory animals both acutely and chronically [21]. An analysis of this study suggests that the combination of DBTC and ethanol might be expected to show enhanced toxic effects on other body organs and systems.

N,N-Dimethyl-*m*-toluamide (DEET) is the active ingredient in numerous commercial mosquito repellants. DEET by itself or as formulated into commercial products permeates through human skin. Dermal exposures to DEET and to mixtures containing DEET have been associated with toxic encephalopathy in children [22]. It has been shown that ethanol, the solvent for DEET, significantly enhances the permeation of DEET through the skin [23]. Toxic effects attributed to DEET absorption may, therefore, be enhanced by the incorporation of ethanol into commercial product formulations.

Ethanol is frequently consumed with other recreational drugs. Cocaine abuse has resulted in an increase of catastrophic cardiovascular events such as myocardial infarction, ventricular arrhythmias, angina pectoris, and sudden death. Many of those so affected also consume ethanol prior to cocaine use. The drug combination of ethanol first followed by cocaine use has been shown to generate synergistic cardiovascular effects in humans and animals [24–27]. The findings are believed to be due to the inhibition effect of ethanol on cocaine metabolism [28].

The addition of ethanol consumption to cocaine use also increases the toxicity of cocaine to human hepatocytes. It is reported that this effect is the result of a depletion of hepatocyte GSH by ethanol, thereby increasing the sensitivity of human hepatocytes to cocaine-induced oxidative damage [29].

Ethanol also enhances the effects of marijuana smoking. The blood levels of THC and subjective mood states of human volunteers were increased by the combination of marijuana smoking and ethanol consumption relative to marijuana smoking alone. The volunteers reported that the marijuana effects were noted more rapidly when co-consumption took place. The accelerated subjective effects corresponded to high plasma THC levels following co-consumption of the two drugs. The authors of the study suggest that the enhanced effects were due to ethanol increasing the absorption of THC [30].

15.6 Ethanol and Cancer

Although ethanol itself is not carcinogenic, chronic consumption of ethanol increases the risk of some cancers. These include cancer of the throat, esophagus, pancreas, small intestine, colon, and liver [31].

In an elegant study, Couch and Baker studied the effects of addition of ethanol to known carcinogens on the cytotoxicity of hamster cells. 1-Methyl-3-nitro-1-nitrosoguanidine (MNNG) is an alkylating agent that covalently bonds to DNA. The cytotoxicity of MNNG was significantly increased when cells were co-treated with ethanol. 4-Methyl pyrazole (MPZ) is a known inhibitor of ethanol metabolism. When the experiments were repeated with MPZ added, ethanol did not enhance the cytotoxicity of MNNG. In a second group of experiments, the combination of ethanol with other carcinogens (4-nitroquinoline-*N*-oxide, mitomycin C, 6-chloro-9-(3-[2-chloroethyl]aminopropylamino)-2-methoxyacridine, and ethyl methanesulfonate) increased cytotoxicity. The proposed mechanism for the effects noted is the impairment of the DNA repair process by acetaldehyde, the product of ethanol metabolism. This is supported by the elimination of the effect of ethanol when MPZ was present, thereby inhibiting the production of acetaldehyde [32].

Heavy alcohol consumption, viral hepatitis, and diabetes are established risk factors for HCC. There is significant synergy for HCC risk in those who have diabetes and are heavy consumers of ethanol, in those who have viral hepatitis and are heavy consumers of ethanol, and in those who have viral hepatitis and diabetes. No mechanism has been proposed for the synergistic risks associated with heavy ethanol consumption, viral hepatitis, and diabetes [33, 34].

15.7 Tobacco Toxicity: Introduction

Cigarettes, cigars, pipe tobacco, and smokeless tobacco are made up of dried tobacco leaves and hundreds of other components added for flavor and other properties. More than 4000 individual toxic lipophilic and hydrophilic chemical compounds, of which greater than 60 are carcinogens, have been identified in tobacco and tobacco smoke [35, 36]. Accordingly, all tobacco and tobacco smoke exposure is, of necessity, to mixtures of toxic chemicals.

Tobacco and tobacco smoke exposure has been identified with numerous health effects. Each year, almost 450,000 people in the United States and an estimated 6 million people worldwide (one in every 6 s) will die from tobacco use [37]. Smoking is the cause of at least 30% of all cancers and 87% of lung cancers [38, 39]. Table 15.1 lists the cancers that are attributed to cigarette smoking and occupational asbestos exposure [38–41].

Cancers attributed to cigarette smoking are:

- Lung
- Oral cavity
- Pharyngeal
- Laryngeal

Table 15.1 Lung Cancer Risks Associated with Tobacco Smoking and Occupational Asbestos Exposure

Exposures	Relative Risk for Lung Cancer
Did not work with asbestos	1.00
Did not smoke	
Worked with asbestos	5.17
Did not smoke	
Did not work with asbestos	10.85
Did smoke	
Did work with asbestos	53.24
Did smoke	

- Esophageal
- Kidney
- Liver
- Pancreatic
- Bladder
- Stomach
- Colorectal
- Cervical
- Ovarian
- Breast
- Prostate
- Brain
- Leukemia.

Cancers only account for about half of the smoking-related deaths. Smoking is a major cause of bronchitis, emphysema, heart disease, and stroke. Tobacco is associated with female reproductive health, increases in miscarriage rates, early delivery, stillbirth, infant death, and low birth rate. Maternal smoking has been linked to adverse neurodevelopment including ADHD in children exposed to tobacco smoke in utero [42, 43]. It is estimated that 9 million Americans suffer from tobacco-related illnesses at any given time [44]. Smoking inhibits an enzyme responsible for regulating the body’s response to inflammation [45].

Passive smoking (also known as secondhand smoke, or ETS) has been shown to produce the same health effects on those exposed to it as to actual smokers, albeit to a lesser degree [46, 47]. ETS is responsible for approximately 3000 lung cancer deaths in the United States annually [48], increases the risk of stroke [49], risk of myocardial infarction and other cardiovascular diseases [50, 51], and impacts respiratory health in those exposed [52]. The cardiovascular effect of secondhand tobacco smoke is illustrated by the drastic reduction of acute myocardial infarctions (heart attacks) noted in Helena, Montana when public smoking was banned [53]. This is discussed more thoroughly in Section 29.4.

Passive cigarette smoke exposure is also associated with psychological distress and risk of future psychiatric illness in healthy adults [54].

Recently, a phenomenon labeled thirdhand smoke has been attributed to the reaction of nicotine with ambient nitrous oxide on environmental surfaces to produce the carcinogenic nitrosamines. Surfaces shown to promote nitrosamine include ubiquitous cellulosic material [55].

It should be noted that the deleterious health effects that result from tobacco use are independent of the form in which the tobacco is used. Thus cigarette smoking, cigar smoking, pipe smoking, chewing tobacco, and snuff inhalation have been shown to produce many of the same adverse health outcomes in people [56, 57].

15.8 Tobacco and Cancer

BaP, a PAH, has long been established as a carcinogen, although one of its diol epoxide metabolites, BPDE-2, is considered the ultimate carcinogen. This is based on the bonding of BPDE-2 to DNA, mutagenicity, and extreme pulmonary carcinogenicity in newborn mice. Although PAHs are considered the primary carcinogens in cigarette smoke, their concentration in condensed smoke is too low to account for the production of skin tumors. Several components of cigarette smoke, e.g., catechol, are co-carcinogenic when applied to animal skin with PAHs [58].

The formation of ROS is considered by many to induce cancer since ROS induces DNA strand breakage. Many components of cigarette smoke tar (the solid phase of cigarette smoke), including polyphenols, have been demonstrated to produce ROS. The combination of polyphenols and nicotine has been shown to act synergistically to produce ROS [59]. Synergistic effects on DNA strand breakage have also been demonstrated by the combined actions of cigarette tar extract and nitric oxide (one of the components of the gas phase of cigarette smoke) [60]. Smoking has been linked to epigenetic effects, such as methylation, which alter gene expressions of 323 genes [61, 62].

The question of whether the induction of cancer in man by cigarette smoke results from the action of a single carcinogen or the action of more than one carcinogen has not yet been resolved. It is known, however, that tobacco smoking is a cofactor in occupational cancers.

15.9 Tobacco Smoke Mixtures

The complexity of tobacco smoke makes it difficult to ascribe a particular health effect to a single component, though some inroads have been made in this regard. Complicating matters further is the fact that human exposure to tobacco smoke is almost never without co-exposure to other toxic chemicals. It is known, however, that when individuals are co-exposed to tobacco smoke and other chemicals not contained in the smoke, health effects are observed that are different from those seen from tobacco smoke exposure only. The remainder of this chapter is devoted to the health effects caused by the combined exposure to tobacco smoke and other chemicals.

15.10 Tobacco Smoke Mixtures and Lung Cancer

Tobacco smoking is the major cause of lung cancer, accounting for almost 90% of all lung cancers. Lung cancer risks for smokers, however, increase dramatically when smokers are exposed to other lung carcinogens.

15.10.1 *Smoking and Uranium*

The lung cancer risk for uranium miners who smoke is much higher than that for uranium miners who do not smoke. This epidemiological finding is supported by laboratory experiments that show an increased incidence of pulmonary tumors in hamsters simultaneously exposed to BaP and alpha radiation relative to exposure to the PAH or the radiation alone [63].

15.10.2 *Smoking and Asbestos*

Tobacco smoking alone [38, 39] and exposure to asbestos alone [64, 65] are risk factors for developing lung cancer. The combination of smoking and working with asbestos carries a multiplicative risk for developing lung cancer. The data in Table 15.1 clearly illustrate this point [66].

The mechanism for the synergism between asbestos and cigarette smoke is not known. It is thought that the iron contained in asbestos may catalyze the formation of hydroxyl radicals from H_2O_2 contained in cigarette smoke [67, 68]. It has also been found, however, that ceramic fibers as well as asbestos fibers have a synergistic effect on the formation of tumor necrosis factor (an indicator of carcinogenesis) by alveolar macrophages in rats [69]. A possible mechanistic explanation is that the solid, insoluble fibers serve as active surfaces for the adsorption of carcinogenic molecules.

15.10.3 *Smoking and Chromium*

Chromium(VI) is a well-known human carcinogen and occupational exposure to it is strongly associated with lung cancer. Tobacco smoking is the major cause of lung cancer, accounting for almost 90% of all lung cancers. PAHs are considered the major lung carcinogens in tobacco smoke. Together, chromium(VI) and PAHs act synergistically and account for the high incidence of lung cancer in those exposed to both agents. It has been shown that chromium(VI) exposure greatly enhances the mutagenicity and cytotoxicity of PAHs by inhibiting the cellular nucleotide excision repair [70].

15.10.4 *Smoking and Radon*

Radon present in indoor air is a known lung carcinogen. It is estimated that between 1% and 5% of all lung cancers can be attributed to radon inhalation in a dose-response relationship [65, 71–73]. Radon and cigarette smoking, however, have a multiplicative synergistic effect on lung cancer rate [74]. No mechanism has been proposed for the observed combined effect of the two carcinogens, though increase in ROS caused by radon decay coupled with that induced by tobacco smoke may be a factor.

15.11 Noncarcinogenic Tobacco Smoke Synergism

Mixtures of tobacco smoke and other chemicals induce health effects that are not limited to carcinogenesis. The following effects are illustrative.

15.11.1 Smoking and Elevated Cholesterol

Tobacco smoking alone greatly enhances the risk for coronary heart disease (CHD) [50]. Smoking and elevated serum cholesterol level synergistically increase the levels of CHD observed [75]. No mechanism for the synergism was proffered by the study.

15.11.2 Smoking and Coke Oven Emissions

Coke oven workers are at risk for developing COPD. There is a dose-dependent relationship between exposure to the benzene-soluble fraction of coke oven emissions and COPD. Smoking in coke oven workers synergistically increases the incidence of COPD [76]. Though many of the compounds in cigarette smoke are identical to those in coke oven emissions, that alone cannot account for the observed synergism.

15.11.3 Smoking and Dairy Farming

Dairy farmers have high incidences of cough, phlegm production, and chronic bronchitis. They are exposed to numerous irritants, allergens, including grain dust and other particulates, airborne bacteria, and chemicals that target the respiratory system. Though smoking alone is associated with the same symptoms, the combination of dairy farming and smoking synergistically elevates chronic cough [77].

15.11.4 Smoking and Wood Smoke Exposure

Smokers who are also exposed to wood smoke, either through home cooking and heating or via environmental pollution, have an increased risk of COPD [78]. Wood smoke contains many of the same toxicants found in cigarette smoke.

15.11.5 Smoking and Bacterial Infections

Mucin is the primary component of mucous. Factors associated with COPD, such as bacterial infections and cigarette smoke, individually induce respiratory mucin production in vivo and in vitro. Cigarette smoke, in combination with bacterial infection, synergistically induces the hyperproduction of mucin in those with COPD [79].

15.11.6 Smoking and Organic Solvent Exposure

Smoking enhances the immunotoxicity of aromatic solvents. Tobacco smoke and organic solvents acting alone are immunotoxins that reduce antibody levels in blood

serum. The reduction of serum IgA, IgG, and IgM levels are enhanced (relative to solvent or smoking effects alone) when smokers are occupationally exposed to benzene and its homologs [80].

15.11.7 Smoking and Alcohol Abuse

Ethanol consumption and tobacco use are correlated. Ethanol consumers smoke more than nonsmokers and smokers are more likely than nonsmokers to consume ethanol [25, 81]. Cardiovascular, immunological, and carcinogenic effects are enhanced by the co-consumption of ethanol and tobacco. The following studies illustrate this fact.

Human volunteers who were pretreated with nicotine via a transdermal patch and then consumed ethanol reported that ethanol's effects (feeling drunk and euphoria) were enhanced relative to those not pretreated with nicotine. It was found that heart rates were increased by nicotine and that ethanol-induced heart rates were further increased by nicotine. The authors conclude that the results of this study may help explain the high prevalence of the combined use of ethanol and tobacco [81].

In a laboratory study, mice that were pre-exposed to cigarette smoke had increased levels of lipid peroxidation in their hearts. These levels were further increased in animals co-exposed to ethanol. There were decreases in GSH levels in animals exposed to cigarette smoke and greater GSH decreases in those co-exposed to cigarette smoke and ethanol. The authors conclude that ethanol potentiates the cigarette smoke-induced peroxidative damage to the heart and thereby lowers the cardiac antioxidant defense system [82].

A canine study showed that cardiovascular excitatory effects were synergistically increased by a combination of ethanol and nicotine relative to nicotine alone. Ethanol alone had minimal cardiovascular effects under the conditions of the study [25].

In an *in vitro* study involving human lymphocytes, it was demonstrated that ethanol and nicotine, at non-inhibitory levels when added alone, showed significant suppression of NK cell activity when added combined. NK cell activity is crucial to good health. The authors conclude that the immunological suppression effects of the ethanol/nicotine mix may have clinical implications [83].

Heavy smoking and excessive ethanol consumption are the primary risk factors for upper digestive tract cancers. The cancer risk is dose-dependent, and the combination of ethanol consumption and tobacco smoking acts synergistically and multiplicatively to increase the risk of cancer in abusers [84]. Ethanol alone is not a carcinogen, though its metabolite, acetaldehyde, is a local carcinogen in humans. One study examined the combined effect of ethanol ingestion and tobacco smoking on acetaldehyde levels of *in vivo* saliva levels of human volunteers. It was found that those who actively smoked while being challenged with ethanol had seven times higher *in vivo* salivary acetaldehyde levels than nonsmokers. The study concludes that the markedly increased levels of acetaldehyde may explain the synergistic and multiplicative risk effect of upper gastrointestinal tract cancers in those who drink and smoke heavily [85, 86].

15.12 Summary

Ethanol and tobacco are used recreationally worldwide by millions of people. Ethanol is a single compound with well-known toxic effects. It, however, combines with other environmental toxicants to produce toxic effects that often are not predictable.

Tobacco products and tobacco smoke contain thousands of individual toxic compounds. Some of these chemicals have known toxicities, but the mixture produces effects that are often not anticipated from the toxicology of the single compounds. When mixed with other chemicals, tobacco and tobacco smoke have been shown to produce synergistic toxic effects. When combined with each other, ethanol and tobacco produce highly toxic mixtures that attack the respiratory, gastrointestinal, and immunological systems in man with toxic and carcinogenic effects. Abusers of ethanol injure their own bodies only, while tobacco users also poison others who are unfortunate enough to inhale their smoke. It should be noted that the toxic effects induced by both ethanol and tobacco smoke can be entirely prevented by the cessation of their use. This cannot be said for other toxins that permeate our environment. Finally it should be noted that many deleterious effects of alcohol, tobacco, and mixtures containing these are being discovered and remain to be discovered at this time. For example, it has been recently shown that smokers have significant brain structure abnormalities [53], that cigarette smoking results in lower IQ scores among smokers compared to cohorts who do not smoke [87], and that children who are exposed to secondhand smoke have poorer mental health [88].

The extent of damage to human health and mechanisms of action can be seen from recently published data collected by researchers, the Surgeon General of the United States and the World Health Organization [89, 90]. The reader is referred to the two references just cited for details.

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16 Electromagnetic Radiation and Toxic Exposure

Chapter Outline

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16.1 Introduction

The effects of ionizing radiation have been well known since the time of Marie Curie's death following her Nobel Prize winning experiments. The effects of nonionizing radiation have also been extensively studied, but the literature is replete with conflicting findings of the effects of exposure. The effects of combined co-exposure to radiation and toxic chemicals have not been well examined, but the limited experimental work that has been carried out in this area suggests that synergism is to be expected. It is thought that much of the conflicting experimental results and empirical observations may be due to co-exposure to electromagnetic radiation (EMR) and toxic chemicals. This chapter examines the subject of the combined effects of radiation and toxic chemical exposure.

The effects ascribed to only EMR will be briefly mentioned, but not discussed in detail. Thousands of learned articles on this subject have been published in print journals and on the internet.

EMR is not a "chemical" per se, and the following sections that discuss mixtures of EMR and toxic chemicals do not mean to imply so. What is meant here by the term "mixture of EMR and toxic chemicals" is the simultaneous (or close in time) exposure to EMR and a xenobiotic chemical. The interaction between the xenobiotic species and EMR can occur in one of the following three different ways:

1. EMR activates the xenobiotic to a form that reacts with endogenous molecules.
2. EMR activates an endogenous molecule to a form that reacts with the xenobiotic.

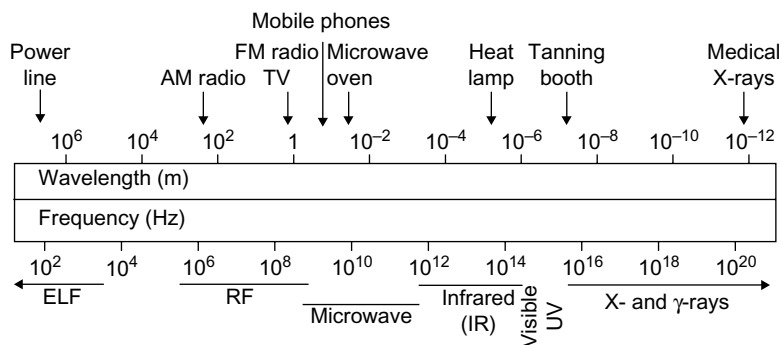


Figure 16.1 The electromagnetic spectrum.

- Both the endogenous molecule and the xenobiotic are activated by EMR and reaction between the activated species occurs.

Many of the interactions between xenobiotics and EMR occur via unknown mechanisms. What is known, however, is that free radicals and ROS play large roles in the toxicities of EMR/chemical mixtures. This will be discussed in the following sections.

16.2 The Electromagnetic Spectrum

Figure 16.1 shows the electromagnetic spectrum and the applications of EMR at various frequencies.

Biological effects of EMR are best ascribed to four regions of the spectrum and are as follows:

- Ionizing:** This is the high-frequency area of the spectrum where chemical bonds are broken and direct damage to cellular destruction occurs. Examples are gamma radiation and X-rays.
- UV (wavelengths of 290–420 nm):** The spectral region where multiple bonds are cleaved and free radicals are formed. Cellular damage may occur on prolonged exposure or via excitation of phototoxic and photoallergic species. Examples are prolonged exposure to sunlight or tanning lamps.
- Microwave and radiofrequency (RF):** The spectral region where cellular heating is induced. Examples are microwaves and radio transmissions.
- Power frequency:** The spectral region where energies are sufficiently low so that cellular heating is not readily induced. The most common and most studied example is that of electrical power-line-generated waves.

16.3 Ionizing Radiation and Toxic Chemical Mixtures

Ionizing radiation is an effective killer of micro-organisms and cancerous tissue. Accordingly, it is used to sterilize medical devices, to irradiate food, and to treat

tumors. Ionizing radiation includes emissions from radioisotopes and X-rays. X-rays have numerous beneficial uses and are tolerated well by humans in small doses. It is well known that exposure to excessive quantities of ionizing radiation can induce mutations and carcinogenesis and, in the extreme, causes death.

Exposure to ionizing radiation and some chemicals induces unanticipated effects. The following are examples of such interactions.

Simultaneous exposure to 1,2-dibromoethane and low doses of X-rays has been shown to induce somatic mutations. The authors of the study ascribed this synergistic effect as due to single-strand lesions in the DNA [1].

Temozolomide, a chemotherapeutic drug used to treat cancerous human brain tumors, enhances radiation response in human glioblastoma cells when concurrently administered with radiation. This effect has been shown to increase the degree of radiation-induced double-strand DNA damage [2].

Interleukin-13 (IL-13) receptor-targeted cytotoxin is highly toxic to human glioblastoma cells (GMB). Prior irradiation of GMB cell lines followed by the administration of IL-13 does not enhance cytotoxicity. Concomitant treatment of radiation with IL-13, however, produces greatly enhanced cytotoxic effects [3]. No mechanism for the observed synergism was offered by the study's authors.

A synergistic anti-tumor effect was observed in human chronic lymphocytic leukemia cells when treated with radiation and a combination of 2'-deoxycoformycin and deoxyadenosine. The effects noted were greater than the predicted additive ones. Synergism was enhanced by increasing radiation or by raising the concentration of deoxyadenosine. The authors of the study concluded that the combination of 2'-deoxycoformycin and deoxyadenosine acts as a radiosensitizer [4].

The studies just noted, as well as others that are similar in nature, point out the synergistic effects observed when ionizing radiation is co-administered with toxic chemicals. Though most of the studies found in the literature were designed to address the issue of combating carcinogenesis, it should be noted that combinations of ionizing radiation and toxic chemicals can produce adverse effects in healthy tissues and that intentional exposure to ionizing radiation (e.g., X-rays) can prove to be more toxic than anticipated when one is simultaneously exposed to toxic chemicals [1].

16.4 UV Radiation and Toxic Chemical Mixtures

UV radiation from the sun that impinges upon the earth's surface is in wavelengths between 290 and 400 nm. UV radiation that reaches the earth's surface is classified as UVA (long length waves of 320–400 nm) and UVB (short length waves of 290–320 nm).

UVA plays an essential role in the formation of vitamin D by the human skin, but is harmful by causing sunburn and cataract formation in the eyes. As will be seen later, UVA also causes toxic effects when mixed with xenobiotic chemicals. UVB causes damage at the molecular level. It is absorbed by DNA and alters its structure. UV radiation excites organic molecules and generates free radicals which are responsible for substitution, elimination and polymerization reactions, free-radical

formation, and generation of ROS. Exposures to both UVA and UVB concurrent with exposures to xenobiotic chemicals produce unanticipated toxic effects. The following are examples of the mixture effects of UV radiation.

Both hydrogen peroxide and UV radiation kill bacterial spores. When applied together, however, they act synergistically. The mechanism for this synergism is not proven, but thought to involve free-radical formation [5]. A similar synergism was observed between ozone and UV radiation. While ozone is a stronger disinfectant than UV radiation, coupling ozone with UV radiation was more effective than ozone or UV radiation alone. The authors of this study attributed the synergistic effect to the generation of hydroxyl radicals by ozone photolysis [6].

Inorganic arsenic is an established human carcinogen. Though the mechanism of the induction of cancer is largely unknown, epidemiological studies suggest that the combined action of arsenic and UV radiation increases the cancer risk. A recent study has shown that pretreatment of human lymphoblastoid cells *in vitro* with arsenic(III) followed by UV radiation exposure resulted in the inhibition of the repair of UV-induced pyrimidine dimer-related DNA damage and thereby enhanced mutagenesis [7].

Retinol (an isomer of vitamin A) is regularly used as a supplement to combat various illnesses in humans. UV radiation exposure results in the generation of free radicals, oxidative damage to biomolecules, and decreased cellular viability in cultured mammalian cells. Co-treatment of cells with retinol and UV radiation resulted in significant increases in UV-mediated free-radical formation, lipoperoxidation, DNA fragmentation, and mitochondrial oxidative damage relative to UV treatment alone. Retinol, rather than protecting against free-radical generation, enhances UV-mediated oxidative damage. The authors of the study suggested that retinol-enhanced uptake of iron increases ROS generated by the Fenton reaction (see Section 4.9) and acts synergistically to cause oxidative damage to cells [8].

UV radiation is known to induce non-melanoma skin cancer. Ethanol and aloe emodin alone do not induce skin tumors in the absence of UV radiation. When an ethanol solution of aloe emodin was painted onto the skin of mice in conjunction with UVB exposure, the mice developed melanin-containing skin tumors. The mechanism for the observed carcinogenesis induction by the mixture is unknown [9].

UV radiation exposure is known to induce photosensitive responses in humans. Photosensitivity is an adverse reaction that occurs when a chemical or drug is applied to the skin or taken internally at the same time when one is exposed to UV radiation. Not all people are photosensitive to the same agents. Two distinct responses are observed: phototoxic and photoallergic reactions.

Phototoxicity is photosensitivity that is independent of immunological responses. Phototoxic responses are dose dependent and will affect almost anyone when sufficient dosage is applied or when taken concurrent with UV exposure. In phototoxic reactions, photoactivated chemicals cause direct cellular damage. UV absorption produces either excited state chemicals or metabolites of these chemicals. These, in turn, can be converted into either free radicals or singlet oxygen, either of which results in biomolecular oxidation [10].

Photoallergy is immunologically mediated. Photoallergy develops in sensitized individuals and is not dose dependent, though higher doses of photoallergens

Table 16.1 Illustrative Examples of Photosensitizing Products

Industrial chemicals
Agricultural chemicals
Artificial sweeteners
Petroleum products
Deodorants
Hair sprays
Makeup
Fragrances
Antibiotics
Antihistamines
Antifungals
Cardiovascular medications
Diuretics
Nonsteroidal anti-inflammatory drugs (e.g., ibuprofen)
Sunscreens (e.g., PABA)

Source: Ref. [9].

induce stronger reactions. Cross-sensitivity is often observed, where one's photosensitivity to one chemical increases the likelihood of reacting to a second chemical. Photoallergic reactions may not be predictable from a consideration of the chemical(s) to which exposure occurs. Reactions to first exposures of photoallergens and UV radiation are not generally observed, since hypersensitivity responses require immune system activation and hence an incubation period [11]. Once sensitized, subsequent exposures of an individual to the same or another photoallergen can induce a more rapid response [12]. Though photoallergic responses primarily occur on skin areas exposed to UV radiation, they can spread to other areas and produce systemic responses which are often difficult to characterize [13].

Photosensitizers are chemicals that induce photoallergic responses. They include a wide spectrum of chemical products [9]. Table 16.1 lists illustrative examples of photosensitizing products.

Phototoxicity and photoallergenicity reactions to many antibiotics have been reported. The fluoroquinolone group of antibiotics is known to induce both types of reactions when administered to patients who are co-exposed to UV radiation. In one laboratory study, it was demonstrated that, in guinea pigs, administration of a single oral dose of each of seven fluoroquinolones (nalidixic acid, norfloxacin, ofloxacin, enoxacin, ciprofloxacin, lomefloxacin, or tosufloxacin) followed by UVA exposure induced phototoxicity. Photoallergic reactions were also induced for two of these antibiotics (nalidixic acid and lomefloxacin) by an immunoadjuvant (cyclophosphamide) pretreatment followed by UVA exposure. This study demonstrated that clinically observed phototoxicity and photoallergenicity in humans can be duplicated in laboratory animals and suggested that animal testing could be a predictor of human reactions [14].

A number of the tetracycline derivatives are phototoxic. In one study, chlortetracycline, doxycycline, and dimethylchlortetracycline treatment of normal human

skin fibroblasts resulted in total cell death within 14 days when co-administered with UVA. A dimethylchlortetracycline and UVA co-treatment also showed a strong photosensitizing effect in a 7-day-exposure study. These results, too, are consistent with clinically reported reactions in humans [15].

A test on human volunteers showed that doxycycline is a potent photosensitizer. Eight subjects were given the drug for 3 days. On the third day, they were exposed to UVA and UVB and evaluated 24h after the UVA treatment. Four of the eight subjects developed strong sensitizing symptoms [16].

Cultured human urinary bladder carcinoma cells treated with doxycycline and UVA showed mitochondrial damage. Cell membrane integrity was maintained for several hours after mitochondrial damage appeared, indicating that the mitochondrion rather than the cell membrane is an earlier target of doxycycline when irradiated with UVA. The authors of the study opined that the photochemical reaction involves singlet oxygen [17].

Mixtures of pesticides and UV radiation also are phototoxic. Hairless dogs treated with maneb (a fungicide) and UVA showed epidermal degradation, vasodilation, and intradermal infiltration of inflammatory cells. Animals treated with zineb (a general-use pesticide) and UVA produced comedones with well-developed pilosebaceous glands [18].

Crude oil on the human skin leads to increased pigmentation and erythema (sunburn) when people are exposed to sunlight. This effect was demonstrated in a laboratory experiment with mice, in which shaved skin treated with crude oil and UVA led to depletion of epidermal Langerhans cells, an important component of immunity within the skin. Treatment with crude oil alone did not result in a decrease of epidermal Langerhans cells [19]. A follow-up study showed that at least one component of crude oil, anthracene, produces the same effect upon co-treatment with UVA [20].

Cosmetic and personal care products are widely used for esthetic purposes. Many cosmetic products are complex mixtures of many chemical species, including some known to be toxic (see Section 11.7). Several studies have identified phototoxic effects that are attributable to cosmetic ingredients. Methylparaben is a widely used preservative in cosmetics. In an *in vitro* test it was shown that methylparaben significantly increased OS, nitric oxide production, and lipid peroxidation when cells were exposed to UVB [21]. The photomutagenic sunscreen, padimate-O (octyl dimethyl PABA), generates free radicals and attacks DNA, producing strand breaks and lesions when illuminated with simulated sunlight on cells *in vitro*. Such an ingredient in sunscreens, while preventing sunburn, contributes to sunlight-related cancers [22, 23]. Another ingredient of sunscreens, titanium dioxide, absorbs about 70% of incident UV radiation. In aqueous solutions, this UV absorption leads to the generation of free radicals and damages human cells both *in vitro* and *in vivo* [24]. Petrolatum and basis cream are commonly used skin emollients. In a human volunteer test it was shown that both increase the minimal erythema dose upon exposure to UV radiation [25]. Two popular skin-conditioning compounds, azulene and guaiazulene, are not mutagenic when tested in the absence of light, but decidedly so when mixed with UV and visible light [26]. It is clear that those who formulate cosmetic products must be careful to exclude phototoxic chemicals, since exposure to sunlight is inevitable following cosmetic application.

16.5 Nonionizing Radiation Introduction

Though it is universally agreed that ionizing and UV radiations are harmful to humans, the question of whether nonionizing EMR is harmful is the one surrounded with controversy. Numerous studies have been carried out showing that exposure to such radiation is harmful and others have reached opposite conclusions. Some studies that have demonstrated harmful consequences of exposure could not be duplicated in other laboratories. Most of the studies to date have been aimed at addressing radiation exposure alone. Only a relatively few studies have addressed the effects of mixtures of toxic chemicals and nonionizing radiation. These studies, however, offer valuable insights and suggest that the spurious results found in the radiation-only research may have overlooked co-exposure to chemicals.

Nonionizing radiation consists of parts of the electromagnetic spectrum that correspond to microwaves, also identified as RF waves and extremely low-frequency waves (ELF). RF waves range from 300MHz to 30GHz and correspond to AM radio, FM radio, TV, mobile telephone, and microwave oven transmissions. ELF waves are in the range of 50–60Hz and correspond to electrical transmission power-line emissions.

In a recent study it has been reported that microwaves from mobile telephones show stronger effects in stem cells than in differentiated cells. These waves cause double-strand DNA breakage in stem cells but not in differentiated ones. The authors concluded that this effect may be important for cancer risk assessment [27].

16.6 RF Radiation and Toxic Chemical Mixtures

RF radiation is harmful to human tissue when converted into heat following absorption. As a result, the amount of RF energy absorbed is critical to ascribing damage. Whole-body average specific absorption rate (SAR) is used to quantize the amount of RF that is absorbed. SAR is expressed in watts per kilogram (W/kg). Biological effects occur at SAR of 1 W/kg or greater in adults and children. RF radiation exposures of less than 1.0 SAR are generally considered safe [28].

Human exposures to RF radiation arise from military use, industrial use, broadcasting, and cellular phone use. These exposures have been linked to increased numbers of SAB, neurological effects, altered red and white blood cell counts, increased somatic mutation rates in lymphocytes, cardiovascular effects, increased cancer risk, and increased childhood cancers [29–32]. Other studies, however, have refuted these findings [28, 33–35]. As stated in the introduction, only a relatively few studies addressed the combined effects of toxic chemical and RF exposure. A thorough search of the literature shows that such studies have not been refuted. The following are illustrative examples of these mixture studies.

The combination of chromium trioxide and RF radiation has synergistic mutagenic effects upon *Vicia faba* root-tip cells upon exposure. Mutagenesis is sharply elevated relative to treatment with chromium trioxide alone [36].

Combined exposure to RF and the glycol ether, 2-methoxyethanol (2-ME), produces increased teratogenicity in rats. Combined exposures enhance the adverse effects produced by either RF or 2-ME alone [37, 38]. Though other glycol ethers have not been so tested to date, many widely used glycol ethers are structurally similar to 2-ME and may also have teratogenic effects when exposures to these are concurrent with RF.

Mitomycin C (MMC) and 4-nitroquinoline-1-oxide (4NQO) are known to be mutagenic to human lymphocytes. When cells were exposed to each of these and RF, synergistic effects were observed. DNA damage was greater than that observed for MMC or 4NQO alone [39].

Tumor formation is generally regarded as involving an initial damage to DNA by mutagenic chemicals or ionizing radiation followed by a second step in which non-mutagenic promoting agents promote tumor formation. Tumor promoters include DDT, PCBs, saccharin, and phorbol esters (plant lectins). Nonionizing RF radiation alone is not known to promote carcinogenesis. In combination with phorbol esters, however, RF does promote cancer [40, 41]. It has also been shown that phorbol ester treatment of embryonic fibroblasts that have been previously irradiated with X-rays (ionizing) and microwaves (nonionizing) increases transformation frequencies to rates greater than those observed when pre-irradiation is only with X-rays under the conditions tested [42]. These findings strongly implicate the carcinogenicity of RF/toxic chemical mixtures.

16.7 ELF Radiation and Toxic Chemical Mixtures

All electrical devices generate ELF electromagnetic waves in the range from 50 to 60 Hz. Epidemiological studies have associated environmental exposure to ELF waves with human malignancies, including leukemia, in children living close to high-tension-power lines, and brain cancer [43–46]. Other studies have refuted these findings [47–50]. As best as can be determined, none of these studies considered co-exposures to chemical agents.

One theory of the connection between ELF exposure and cancer suggests that ELF alters certain cellular processes that subsequently lead to strand breaks in DNA and other chromosomal aberrations. This theory is based upon free-radical production caused by acute and chronic ELF exposure. It opines that acute exposure can lead to phagocytosis and consequently free-radical production, macrophage activation and direct stimulation of free-radical production, and an increase in the lifetime of free radicals and that long-term exposure can lead to chronically increased free-radical levels [51].

It is generally accepted that magnetic fields at flux densities below 2 tesla (T) do not induce adverse health effects [50]. This is refuted by a recent study that reported a 50-Hz ELF of strength 1 mT is genotoxic to cells *in vitro* [52]. This study did not consider co-exposures to chemicals.

Several studies have been carried out on mixtures of ELF and toxic chemicals that demonstrate the combined toxicities. Illustrative examples are as follows.

Environmental magnetic fields (1.2 μ T, 60 Hz) significantly reduce the inhibitory action of physiological levels of the hormone melatonin on the growth of human breast cancer cells in vitro. A similar inhibitory effect is also found from the exposure of these cells to a pharmacological level of the cancer inhibitor tamoxifen and the same ELF [53]. This study was reproduced by a second team of researchers with identical results [54]. Both sets of authors concluded that environmental-level magnetic fields can act to modify the action of a hormone or a drug on the regulation of cell proliferation.

Benzene is a known leukemogen. It is widely accepted that benzene's metabolites are the ultimate leukemogens. An in vitro study showed that co-exposures to the benzene metabolite, hydroquinone, and ELF (50 Hz, 1 mT) produced a clear genotoxic effect. Co-exposure to the same ELF and 1,2,4-benzenetriol (BTL) led to a marked increase in the genotoxicity of BTL [55]. In a second in vitro study, ELF (50 Hz, 5 mT) plus MNNG or 1,4-benzenediol (BD), both known carcinogens, were shown to increase the extent of DNA damage relative to MNNG and BD alone. Under the conditions of testing, ELF alone did not cause primary DNA damage [56].

A study, in which human peripheral blood leukocytes from four different donors were exposed to ELF (at 3 mT) plus the genotoxic xenobiotics MNNG and 4NQO, found that ELF increased the primary DNA damage of both MNNG and 4NQO. In this study, ELF alone did not cause primary DNA damage [57].

Metal-mediated formation of free radicals causes modifications in DNA bases, enhanced lipid peroxidation, and altered calcium and sulfhydryl homeostasis, and is attributed to increases in ROS [58]. In one study, rat lymphocytes incubated with low concentrations of ferrous chloride (10 μ g/mL) alone did not produce detectable DNA damage. Exposure of these lymphocytes to ELF (50 Hz, 7 mT) alone also did not increase the number of cells with DNA damage. When cells were simultaneously exposed to both iron and ELF, however, the number of damaged cells was significantly increased. The authors hypothesized that the reason for the increased damage is that the combination of ELF and iron acts to substantially increase the number of ROS generated relative to iron itself [59].

Not all studies have reached the same conclusions. In an in vitro study of human-hamster hybrid AL cells treated with MNNG and ELF (100 μ T, 60 Hz), the ELF neither alone nor combined with MNNG increased MNNG cytotoxicity. The authors concluded that neither short- nor long-term exposure to EMF alone or in combination with other environmental carcinogens increases genotoxicity [60]. These authors, however, tested only one carcinogenic chemical and applied a magnetic field that was an order of magnitude lower than the strengths of those applied in other studies combining MNNG and ELF that did show genotoxicity [56, 57].

The conflicting results just discussed raise the question of what are safe levels of exposure to ELF, or for that matter UV and RF as well. It is opined here that the answer may lie in a consideration of what chemicals the test organisms were co-exposed to at the time of EMR exposure. Co-exposures could come from xenobiotic species present in the home, workplace or laboratory, environmental chemicals, and/or dietary uptake.

16.8 Summary

It is universally accepted that ionizing and UV EMRs induce toxic effects in humans. It has been shown earlier that these toxic effects are exacerbated when irradiation is coupled with xenobiotic exposure. Conversely, the toxic effects of xenobiotic exposure are enhanced by simultaneous exposure to ionizing or UV radiations.

The question of whether radiowave frequency (microwave range) and ELF radiation alone are toxic to humans remains an open question. What seems clear is that co-exposure of EMR at virtually all frequencies with xenobiotic chemicals increases free-radical formation and OS, with corresponding health consequences.

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Part III

Mixture Effects on Body Systems

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17 Respiratory System

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17.1 Introduction

About 10% of the population of the United States (more than 30 million people, including 10 million children) suffers from chronic lung diseases. Of these, about 12 million, including over 4 million children, experience at least one asthma attack annually [1, 2]. A WHO study in Europe, the International Study of Asthma and Allergies in Childhood (ISAAC), found that the asthma prevalence in children ranged from less than 5% to greater than 20% [2–4]. The results of that study are shown in Table 17.1.

Table 17.1 Prevalence of Asthma in Children Aged 6–7 Years and 13–14 Years

Country	Prevalence in 6- to 7-Year-Old Children (%)	Prevalence in 13- to 14-Year-Old Children (%)
Albania	5	4
Austria	3	15
Belgium	7	8
Estonia	10	9
Finland	—	18
Georgia	7	5
Germany	8	13
Ireland	—	27
Italy	7	8
Latvia	—	11
Lithuania	7	7
Malta	15	14
Poland	13	11
Portugal	13	12
Romania	—	23
Russian Federation	—	12
Spain	9	9
Sweden	11	9
Ukraine	13	21
United Kingdom	25	21

Source: Ref. [3].

The causes for this respiratory disease epidemic include environmental exposures to chemical as well as biological agents [5].

The toxic effects of single chemicals on the respiratory system have been fairly well characterized and are listed in numerous places, as described previously in Section 13.2. Though there is no one list of all respiratory toxins, the Scorecard list contains an extensive list of these and includes references for further investigation [6].

Respiratory effects resulting from exposures to toxic chemicals include irritant responses, sensitization and asthma, COPD, RADS, and cancer. Some chemicals, including isopropanol, MEK, and many hydrocarbons, are respiratory irritants. As will be seen below, exposures to high concentrations of irritants can produce RADS. Other chemicals, including TDI, trimellitic anhydride, and ammonium thioglycolate, are respiratory sensitizers that produce IgE-mediated immunologic responses. Some chemicals, including hexavalent chromium and asbestos, are respiratory system carcinogens.

The effects of single chemicals on the respiratory system will be discussed as background for an understanding of the effects of mixtures. As discussed previously in Section 2.3, unexpected chemical mixture exposure effects are observed when the mixtures contain at least one lipophilic and one hydrophilic chemical. This chapter addresses the effects of chemical mixtures on the respiratory system. Case studies

from the literature with widely different mixture combinations are used to illustrate the effects noted.

Chemicals and chemical mixtures that attack the respiratory system are categorized as corrosives, irritants, and sensitizers. Though the term irritant is often applied in the literature to chemicals that are either corrosives or irritants, the definitions used here are those that follow. These definitions are identical with those used by toxicologists and regulatory agencies to classify the hazards due to chemical inhalation.

Corrosive: A corrosive chemical is one that causes visible destruction of, or irreversible alterations in, respiratory tract tissue upon inhalation of vapors, mists, or fine particulates by chemical action at the site of contact. For most chemicals, corrosivity is a function of concentration. At sufficiently low concentrations, corrosive chemical vapors may act as irritants. Hydrogen chloride, nitrogen dioxide, and sodium hydroxide are examples of chemicals corrosive to the respiratory system.

Irritant: A chemical which causes a reversible inflammatory effect in respiratory tract tissue upon inhalation of vapors, mists, or fine particulates by chemical action at the site of contact. Acetone, ethyl acrylate, and isopropyl amine are examples of respiratory irritants.

Sensitizer: A chemical that causes vulnerable, exposed individuals to develop a respiratory allergic reaction following repeated exposure. Methylene bisphenyl isocyanate, TDI, and trimellitic anhydride are examples of respiratory sensitizers. It should be noted that sensitizing chemicals that are inhaled have the propensity to also induce dermal sensitization and that skin exposure to sensitizers (e.g., ammonium thioglycolate) can induce respiratory sensitization. It has been reported that people with asthma have a higher incidence of food allergies and has been hypothesized that allergic reactions to food may lead to asthmatic attacks [7]. Such cross-sensitization will be discussed later and in Chapter 27.

17.2 Respiratory Irritant Mixtures

This section is devoted to chemical mixtures that are respiratory irritants. Irritants do not induce immunochemical responses, and irritation in non-sensitized individuals generally leads to slower, less serious respiratory responses and usually requires higher doses of toxicants to produce symptoms than in sensitized people. Irritant-induced inflammation responses (e.g., bronchial hyperactivity) can be severe and prolonged but, by definition, do not result in sensitization of those so exposed. Mixtures of lipophiles and hydrophiles induce irritant respiratory system responses at concentration levels that are below those for the single chemicals. This phenomenon is well demonstrated by exposures in “sick buildings.”

Exposures to sick buildings may stimulate respiratory responses in healthy individuals with no previous history of asthma, allergic rhinitis, chronic respiratory disease, recent acute respiratory illness, or extensive exposure to pollutants. Chemicals typically found in sick buildings arise from carpeting, paint, wood products, cleaners, and other sources. These chemicals are mixtures of lipophilic and hydrophilic chemicals, and with the exception of isocyanates from PU wood finishes, are usually

Table 17.2 Chemicals of Exposure in an SBS
Simulation Study on Healthy Volunteers and the
 K_{ow} Values of These Chemicals

Chemical	K_{ow}
<i>p</i> -Xylene	3.15
Styrene	2.95
<i>n</i> -Butylacetate	1.78
<i>n</i> -Butanol	0.88
Ethylbenzene	3.15
<i>n</i> -Hexanal	1.78
Naphthalene	3.30
α -Pinene	4.83
D-Limonene	4.57
1-Decene	5.12
<i>n</i> -Hexane	3.90
<i>n</i> -Nonane	4.76
<i>n</i> -Decane	5.01
Ethoxyethylacetate	0.59
1,1-Dichloroethane	1.79
<i>n</i> -Undecane	5.74
Isopropanol	0.28
Cyclohexane	3.44
1,2,4-Trimethylbenzene	3.63
<i>n</i> -Propylbenzene	3.69
2-Butanone	0.29
<i>n</i> -Pentanal	1.31
3-Methyl-2-butanone	0.84
4-Methyl-2-pentanone	1.31
1-Octane	5.18
Formaldehyde	0.35
2-Butoxyethanol	0.83
Acetone	-0.24
Acetic acid	-0.17

Source: Refs [8, 9].

respiratory irritants that are present at levels far below the TLVs for the individual species and far below total VOC exposures that are deemed hazardous [8, 9]. The chemicals, including aliphatic and aromatic hydrocarbons, aldehydes, ketones, alcohols, glycol ethers, esters, and others, are listed in Table 17.2 along with their concentrations in micrograms/cubic meter and their K_{ow} values.

Respiratory irritants are ubiquitous in the modern indoor environment. Most indoor painting is done with water-based paints. These paints contain many VOCs that are respiratory irritants in high concentrations. Painters and others exposed to these paints at levels far below the TLVs of the individual chemicals, however,

often experience irritating effects to their respiratory systems. An examination of the VOCs typically found in the air where water-based paints are used reveals that those VOCs are mixtures of large numbers of lipophiles and hydrophiles. For example, a study of occupational exposure by painters to VOCs from indoor application of water-based paints revealed a complex mixture of aliphatic and aromatic hydrocarbons, ethers, glycols, glycol ethers, alcohols, aldehydes, esters, halogenated hydrocarbons, and ammonia [10]. The compounds found in this and in another similar study [11] are listed along with their arithmetic mean values and K_{ow} values in Table 17.3. Some of the compounds in Table 17.3 are identical with those in Table 17.2, indicating a contribution of VOCs from water-based paints to SBS. It is noteworthy that none of the compounds in Table 17.3 were present at values anywhere approaching their irritant levels and that the total VOCs were also very low.

The respiratory effects of irritant mixtures are not limited to complex ones such as those just described. Volunteers who were exposed to formaldehyde at concentrations as high as 2.0mg/m^3 (greater than the PEL of 1.2mg/m^3) did not experience lower airway irritation [12], yet those exposed to mixtures of formaldehyde ($K_{ow} = 0.35$) and terpenes ($K_{ow} = 2.42\text{--}4.83$) did exhibit symptoms of lower airway irritation [13]. Additional examples of the effects of respiratory irritant mixtures will be presented later in the case study section (Section 17.7) of this chapter.

Respiratory irritant mixtures can arise from environmental chemical reactions. For example, ozone reacts rapidly with terpenes under environmental ambient conditions to produce aldehydes, ketones, and carboxylic acids. Several studies that have been carried out demonstrated that reaction of ozone with α -pinene, D-limonene, and isoprene produce low-level concentrations (at or below NOEL levels) of oxidation products and that along with residual ozone and terpenes act as respiratory irritants [14–16]. Table 17.4 lists the species typically contained in these mixtures along with their K_{ow} values. As can be seen, the mixtures contain lipophiles (residual terpenes) and hydrophiles (the reaction products). Similar results have also been reported for environmental reaction of terpenes with ozone and nitrogen dioxide [14].

Terpenes are widely present in the indoor environment. They are incorporated in cleaners, plastics, adhesives, and other products. Ozone and nitrogen dioxide are common environmental pollutants. The reactions between these species are representative of other reactions that occur in polluted air and the products formed by their reactions help explain why large numbers of people are impacted even when the atmospheric levels of the polluting species are below NOEL levels.

Respiratory irritation by chemical mixtures is not limited to vapors. Mist (a suspension of liquid particles in air) inhalation represents a far greater hazard to the lungs than vapors of the same chemicals because mists deliver much greater quantities of chemicals to the lung surfaces. Though the toxicities of mist mixtures may be the same as those of vapors, the inhalation of far greater amounts of the chemicals multiply the toxic effects [17]. Mist particle diameters are inversely related to toxicity. Smaller diameter mist particles penetrate deeper into the lung, causing greater injury [18]. Many similar products have been found to have different toxicities when applied as aerosols. Investigation has shown that smaller aerosol particle diameters for similar products induce greater toxic effects than larger diameter particles of the same formulation [18].

Table 17.3 VOCs Found in the Air During Indoor Painting with Water-Based Paints

Chemical	K_{ow}
Aliphatic Hydrocarbons	
Methyl-nonane	5.18
Methyl-decane	5.67
<i>n</i> -Dodecane	6.10
Methyl-cyclohexane	3.61
Ethyl-cyclohexane	4.56
Butyl-cyclohexane	5.07
Aromatic Hydrocarbons	
Toluene	2.73
Xylene	3.15
Styrene	2.95
Ethylmethylbenzene	3.66
Trimethylbenzenes	3.63
Propylbenzene	3.69
Diethylbenzenes	3.63
Alcohols and Glycols	
1-Butanol	0.88
Ethanol	−0.31
Isopropanol	0.28
Ethylene glycol	−1.36
Propylene glycol	−0.92
Ethers and Glycol Ethers	
Dibutyl ether	3.21
1-Butoxy-2-propanol	0.98
2-Phenoxyethanol	1.16
Diethyleneglycol monomethyl ether	−1.18
Diethyleneglycol monobutyl ether acetate	1.30
Esters	
Butyl acetate	1.78
Butyl acrylate	2.36
Butyl butyrate	2.83
Butyl methacrylate	2.88
Butyl propionate	2.34
Methylheptyl acrylate	4.09
Methyl methacrylate	1.38
2-Chloroethyl acetate	1.12
Vinyl acetate	0.73
Aldehydes	
Formaldehyde	0.35
Hexanal	1.78
Nonanal	3.27
Miscellaneous	
Ammonia	−1.38
Triethylamine	1.45
Acrylamide	−0.67
Acrylonitrile	0.25
Acrylic acid	0.35
Methacrylic acid	0.93

Source: Refs [10, 11].

K_{ow} values have been added to the literature data.

Table 17.4 Chemical Species Contained in Ambient Mixtures Following Environmental Reactions of Terpenes with Ozone and Their K_{ow} Values

Chemical	K_{ow}
α -Pinene	4.83
D-Limonene	4.57
Isoprene	2.42
Ozone	-0.87
Formaldehyde	0.35
Acetaldehyde	-0.34
Propionaldehyde	0.59
Butyraldehyde	0.88
Valeraldehyde	1.31
Hexanal	1.78
Formic acid	-0.54
Acetic acid	-0.17
Acetone	-0.24
Methylvinyl ketone	0.41
3-Methyl furan	1.91
Methacrolein	0.74

Particulates are another source of respiratory irritation when inhaled. In urban environments, diesel exhaust particles (DEP) and fly ash residue from power plant oil combustion are the main contributors of respirable particulates of less than $10\mu\text{m}$ diameter (PM10). These contain mixtures of lipophiles and hydrophiles including various metals, acid salts, aliphatic hydrocarbons, PAHs, quinones, nitroaromatic hydrocarbons, and aldehydes [19]. Diesel combustion particulates contain large surface areas that can adsorb large quantities of organic compounds and deliver these to respiratory tract tissue. Other inhaled particulates can adhere to lung surfaces and adsorb and bond with other vapors that are inhaled, thereby increasing their toxicities. PM2.5 particulates (those with diameters of less than $2.5\mu\text{m}$) which reach the lower respiratory tract as far as the alveoli are more toxic than PM10 particulates of the same composition [20]. The subject of fine particle toxicity (nanotoxicity) is explored in greater detail in Chapter 36.

Inhalation of particulates is the leading cause of COPD. Tobacco smoke is the primary source of these particulates and is responsible for up to 90% of all diagnosed COPD cases. While smoking cessation at an early stage of the disease generally stops further progression, continued smoking after onset hastens its progression [21]. Inhalation of other particulates, however, is also associated with COPD. Asbestos, coal, cotton, grain, bentonite clay, and other dusts have also been associated with COPD [22]. All of the materials that have been identified as causative agents for COPD are mixtures of large numbers of individual chemicals. As discussed in Chapter 15, tobacco smoke contains more than 4000 individual lipophilic and hydrophilic chemicals, as well as chemically complex particulates. The large number and

chemically varied causative agents for COPD make it difficult to assign a mechanism for the onset of this disease [22].

17.3 Respiratory Sensitization Mixtures

Sensitization to chemicals is defined as changes that occur in the immune system of an individual following exposure to a chemical or chemical mixture that cause that individual's immune system to recognize and respond to the chemical or chemical mixture upon subsequent exposure to it. Such recognition, called hypersensitivity, leads to responses at lower doses and of greater severity than those experienced by non-sensitized individuals to the same chemical(s). Respiratory sensitization manifests itself through bronchial constriction and rhinitis with attendant symptoms of shortness of breath, wheezing, tight chest (asthmatic response), mucous production, sneezing, coughing, and watery eyes (allergic response) [23]. Not all people who are exposed to sensitizing chemicals are sensitized by such exposure. The propensity for sensitization is an idiosyncratic one, with genetics playing a large role in determining who will or will not be sensitized. The mechanism for sensitization is an IgE-mediated one. The reader is referred to the literature for a discussion of the details of the mechanism [24, 25]. The National Research Council monograph on multiple chemical sensitivities offers one of many primers on the subject [24].

Numerous single chemicals are known to be sensitizers. These include isocyanates, anhydrides, amines, metals and metal compounds, and plastics and their monomers. A complete list of these, as well as of biological sensitizers, was compiled by van Kampen et al. [26]. Table 17.5 contains a partial list of single chemical sensitizers.

Inhalation of sensitizing chemicals can lead to dermal sensitization and dermal absorption of sensitizing chemicals can lead to respiratory sensitization. Airway exposure to TDI has been shown to induce dermal sensitization [27] and dermal application of trimellitic anhydride has been shown to induce respiratory sensitization in test animals [28–30]. These results are consistent with the understanding that both respiratory and dermal sensitization are associated with IgE responses.

Respiratory sensitization is not limited to single chemical compounds. Several mixtures have been identified as sensitizers. The following are illustrative.

DEPs are composed of carbon black and adhered lipophilic and hydrophilic compounds that include approximately 18,000 different high-molecular-weight organic compounds, composed of aliphatic and aromatic hydrocarbons, polycyclic aromatic hydrocarbons, polycyclic aromatic sulfur heterocycles, sulfur dioxide, nitrogen dioxide, aldehydes, and carboxylic acids [31–33]. DEPs are sensitizing the respiratory system and have a direct effect on IgE antibody production [34]. Ragweed is a known sensitizer that affects millions of people seasonally when its pollen is released into the air. Although both DEP and ragweed enhance ragweed-specific IgE, the combination of ragweed and DEP exposure produces a synergistic effect that increased ragweed-specific IgE production by 16-fold [35]. In a separate

Table 17.5 List of Single Chemical Sensitizers

Isocyanates	Platinum
Diphenylmethane diisocyanate	Chloroplatinates
Hexamethylene diisocyanate	Tungsten
Methyl isocyanate	Tungsten carbide
Naphthalene diisocyanate	Plastics Monomers
TDI	Ethyl cyanoacrylate
Anhydrides	Methyl cyanoacrylate
Maleic anhydride	Methyl methacrylate
Phthalic anhydride	VC
Tetrachlorophthalic anhydride	Styrene
Trimellitic anhydride	Miscellaneous
Amines	Ammonium chloride
Amino ethyl ethanolamine	Azodicarbonamide
2-Ethanolamine	Basic blue 99 (hair dye)
Ethylenediamine	Chloramine T
4-Methylmorpholine	Diazonium tetrafluoroborate
Piperazine	Ethyleneimine
Metals and Metal Compounds	Ethylene oxide
Chromium(VI) salts	Formaldehyde
Chromium sulfate	Furfuryl alcohol
Potassium dichromate	Glutaraldehyde
Cobalt	Hexachlorophene
Cobalt sulfate	Metabisulfite
Iridium chloride	Ninhydrin
Nickel	Tetrazine
Nickel sulfate	Triglycidyl isocyanurate

challenge study, DEP was shown to induce sensitization to a neoantigen when DEP levels were similar to those typically inspired in the air of Los Angeles, California, in 3 days [36].

Ethoxylated surfactants (ES) are used in household and industrial cleaners, laundry detergents, pharmaceuticals, and cosmetics. ES react with ambient oxygen to form complex mixtures of oxidation products (including hydroxyaldehydes, formaldehyde, and acetaldehyde that are sensitizers) [37]. In one study, pure surfactant was found to show no allergenic activity. Upon standing in air, however, allergenic activity increased as a function of time, as did the concentration of formaldehyde [38]. Though the studies just described were dermal exposure ones, it should be noted that the ES oxidation products are volatile and that many cleaners are applied in aerosol form, making for quite frequent inhalation, given the use of these chemicals. This point is consistent with the observations that many people suffer adverse respiratory reactions while using products containing ES [39].

Platinum salts are known sensitizers. In a study of workers at a platinum refinery, those who smoked were more than five times as likely as nonsmokers to be sensitized [40]. No mechanism has been proposed for this observed effect.

It is clear that environmental pollution plays an ever-increasing role in sensitization and allergy. The dramatic increase in human allergic airway disease in the past 200 years has paralleled the increase in the burning of fossil fuel [35]. In industrialized areas of the world, the prevalence of atopic diseases such as asthma and allergic rhinitis has increased to the point where it afflicts 10–20% of children living in those regions [41]. The mechanism(s) for the onset of these diseases are still being investigated. As was shown above, DEP and ES are sensitizing agents and the mixture of these and pollen synergize the sensitizing process. It is thought that the adsorption of organic molecules to airborne particulates mediates the adhesion of such particles to pollen surfaces, thereby increasing exposure to pollen [42].

17.4 Asthma and Chemical Mixtures

Asthma is a chronic inflammation disorder of the airways that makes the bronchial tubes swell and narrow, producing wheezing, chest tightness, breathlessness, and coughing symptoms. Airway narrowing in asthma is caused by inflammation, bronchospasm, and bronchial hyperactivity. Asthma does not affect the alveoli and is reversible spontaneously and by drug treatment. Asthma is fully reversible and thus is different from COPD and emphysema, which are accompanied by destruction of alveolar walls and are irreversible.

Asthma may be induced by biological allergens such as pollens and animal proteins or by exposures to particular chemical environments. The latter is termed occupational asthma (OA). OA is defined as “a disease characterized by variable airflow limitation and/or airway hyperresponsiveness due to causes and conditions attributable to a particular occupational environment and not stimuli encountered outside the workplace” [43]. The WHO reports that between 2% and 20% of all asthma rates in industrialized nations are due to OA and the U.S. Department of Labor estimates that 11 million workers in a wide range of industries and occupations in the United States are exposed to at least one agent known to be associated with OA [43]. OA may be caused by exposures to sensitizers [44], or by exposures to irritants. Asthma induced by sensitizers is almost always attributable to single chemical species. Exposures to mixtures of sensitizers have predictive additive effects. Irritant-induced asthma can be attributed to single chemical species and mixtures of chemicals. OA is distinguished from RADS in that OA generally ensues after chronic low-level exposures to chemicals, whereas the onset of RADS occurs following single or short-term exposures to high concentrations of chemicals [44]. RADS will be discussed in Section 17.5.

Asthma can be induced by chemicals that are ingested or dermally applied as well as inhaled chemicals. Sulfites in wine, salads, other foods, and some medications are known to induce asthma when ingested [7, 45–47] and many chemicals, including isocyanates and anhydrides, have been shown to induce asthma following dermal exposure [48, 49]. The discussion in this section, however, will be limited to inhaled chemical mixtures as causative agents for asthma.

OA can be induced by single sensitizing chemicals as well as by single irritant chemicals. Sensitizers, all of which are hydrophiles, are listed in Table 17.5. Irritants

Table 17.6 Single Chemicals that Induce OA and Their K_{ow} Values

Chemical	K_{ow}
Ammonia	-1.38
Calcium oxide	-0.87
Chlorine gas	0.85
Formaldehyde	0.35
Hydrochloric acid	0.54
Sodium hydroxide mist	-3.88
Sulfuric acid/sulfur dioxide	-2.20
Titanium tetrachloride	1.47

Table 17.7 Chemical Mixtures that Induce OA

Burnt chlorofluorocarbons	Mixed solvents
Burnt paint fumes	Paint fumes
Carpet emissions	Pesticide sprays
Cigarette smoke	PAHs
Cleaning products	Spray paints
Diesel fumes	Welding fumes
Epoxies	

that induce OA are almost exclusively hydrophilic. Table 17.6 contains a partial list of these [50–54] and their K_{ow} values.

Chemical mixtures that induce OA are almost exclusively combinations of hydrophiles and lipophiles. Table 17.7 contains a partial list of these mixtures [50–56]. Though the precise compositions of all of these chemicals are not given in the references cited, it is possible to extrapolate from the nature of the materials that they contain both hydrophiles and lipophiles. For example, as was shown in Table 17.3, paints contain numerous lipophilic and hydrophilic species.

Many chemical mixtures are known to induce asthma. Illustrative examples of some of these are as follows.

Cleaning products rank at or near the top of chemical mixtures that induce asthma [57]. These products are almost always mixtures of lipophiles and hydrophiles and are formulated that way to insure maximum cleaning power. Chemicals contained in cleaning products include chlorine, acids, alkalis, glycol ethers, ammonia, ethanol, isopropanol, D-limonene, ionic and nonionic surfactants, ethanolamines, phenols, and others. As an example of cleaner toxicity, cleaners commonly used in hospitals have been associated with increased incidences of asthma in workers who clean hospitals [58].

Children exposed to polluted air containing low levels of ozone (hydrophile) and PM2.5 particulate matter (mixture of lipophiles and hydrophiles) are more prone to asthma than those living in areas with clean air [59, 60].

Hairdressers have higher rates of asthma than the general public. They are constantly exposed to persulfates in hair bleaches (hydrophiles) and hair sprays (mixtures of lipophiles and hydrophiles) [61].

Pig farmers have a higher incidence of asthma than the general population. Quaternary ammonium compounds (QACs) are commonly used disinfectants with no known sensitization effects. In a study of Dutch pig farmers it was found that the incidence of asthmatic sensitization was much higher for those who used QACs than for those who did not use these disinfectants [62].

Children who regularly swim in indoor swimming pools have been found to have higher rates of asthma than those who do not. The cause has been attributed to the reaction of disinfectant chlorine (hypochlorous acid) with organic matter (e.g., perspiration, saliva, and urine) to produce lipophilic/hydrophilic mixtures of disinfection by-products that include THMs, trihaloacetic acids, and chloramines that are inhaled by swimmers as vapors and aerosols [63]. Similar increases in asthma prevalence have been reported for lifeguards who work in indoor swimming pools [64].

Tobacco smoke contains hundreds of different lipophiles and hydrophiles. Children and adolescents are particularly sensitive to chemical-induced asthma. One study has found that children and teens who smoke cigarettes have nearly four times the risk of developing asthma in their teens than their cohorts who do not smoke [65].

Cooling, lubricating, and cutting oils and their decomposition products contain large numbers of lipophiles and hydrophiles. Exposure to vapors and aerosols of these products is associated with increased incidences of asthma [66–68].

As discussed in Chapter 14, pesticide products are mixtures of lipophilic and hydrophilic components. In a survey of more than 20,000 farmers who were certified pesticide applicators, it was found that total pesticide usage was related to the onset of wheezing (asthma symptom). It was further found that 19% of all applicators reported wheezing within the year before the survey was taken and that the use of five pesticides in particular demonstrated significant dose–response trends [69]. These pesticides, paraquat, parathion, malathion, chlorpyrifos, and *S*-ethyl-dipropylthiocarbonate, are commonly used by farmers alone and in combination and may account to a significant degree for the increased incidence of asthma among farmers relative to the general population.

Stainless steel welders are at high risk for developing asthma. The fumes emitted into the welders' breathing zones contain hexavalent chromium, iron, nickel, manganese, titanium, molybdenum, copper, and chromium, as well as silica, calcium carbonate, VOCs from fluxes, and fumes from burnt paints [70–75].

Aluminum welding, too, has been shown to be a cause of asthma. Aluminum electrodes used in welding contain chlorides, fluorides, chromium, nickel, lithium, sodium, potassium, and aminoethyl ethanolamine in addition to aluminum [76].

Bronchospasm reactions have been reported following administration of various pharmaceuticals [77]. A partial list of these is given in Table 17.8.

It remains unclear as to whether all the adverse reactions were to the pharmaceuticals themselves or to excipients that are added to most formulations. Adverse reactions have been reported for preservatives (e.g., benzalkonium chloride, parabens, thimerosal), colorants, emulsifiers, and sulfites. Ironically, bronchospasm reactions have been observed following the use of inhaled asthma preparations [77].

Asthma includes a range of different symptoms, among which are wheezing, coughing, chest tightness, and difficulty breathing. The underlying cause of asthma

Table 17.8 Pharmaceuticals Which Have Been Reported to Induce Bronchospasm

Vaccines	Contrast media
Immunoglobulins	Various drugs
Plasma volume expanders	Acetylcysteine
Hormones	Bismuth subcitrate
Vitamins	Etamsylate
CNS agents	Fluvastatine
H1 and H2 receptor antagonists	Pamindronic acid
Local anesthetics	Quinine
Phytomedicines	Tizanidine
Eye medications	Tropisetron
Hydrolyzed proteins	

is inflammation of the airways, but what triggers this inflammation and why some people develop the disease and others do not is not understood at this time. It has been found that NK T cells play an important role in human asthma [78], and it has been recently shown that the enzyme aldose reductase regulates inflammatory reactions [79]. People with asthma have a range of different symptoms and different responses to treatment and, indeed, it has recently been proposed by the medical journal *Lancet* that the term asthma be abolished, since it is unlikely to be a single disease [80]. Asthma has been increasing steadily since the 1980s. It is estimated that between 10% and 25% of adult asthma is related to chemical exposures on the job [81]. The reasons behind the increase of childhood asthma are not fully understood at the time of this writing, but are believed to be strongly related to environmental pollution. In a study published in 2010, it has been found that soot particles spewing from diesel truck exhausts are directly related to the high rates of asthma found in school-aged children in the South Bronx, New York [81].

Though asthma is known to be induced by sensitizing chemicals, it is also triggered by irritant chemicals. Significantly, when asthma is induced by sensitizers, it is almost always done so by exposure to a single chemical, but when triggered by irritants, it is almost always following exposures to mixtures of lipophiles and hydrophiles. This connection also holds for the onset of RADS, which is discussed next.

17.5 Reactive Airways Dysfunction Syndrome

RADS is a type of asthma that develops after exposure to a single environmental or occupational exposure to a high concentration of a single chemical or chemical mixture [82]. Though RADS clinically simulates bronchial asthma and is associated with airways hyperactivity, it is different from OA because of its rapid onset following a single exposure, its lack of a sensitization period requirement, and its occurrence without an allergic or immunologic etiology [83]. Eight clinical criteria for its diagnosis were set down by Brooks, Weiss, and Bernstein, who first coined the term RADS in 1985. These are given in Table 17.9.

Table 17.9 Clinical Criteria for the Diagnosis of RADS

1. A documented absence of preceding respiratory complaints.
2. The onset of symptoms following a single specific chemical exposure.
3. The chemical exposure is to a gas, smoke, fume, or vapor which is present in a very high concentration and has irritant qualities to its nature.
4. The onset of symptoms occurs within 24 h after the exposure and persists for at least 3 months.
5. Symptoms simulate asthma with cough, wheezing, and dyspnea predominating.
6. Pulmonary function tests show airflow obstruction.
7. Methacholine challenge test is positive.
8. Other types of respiratory diseases are ruled out.

Source: Ref. [83].

Table 17.10 Single Chemical Corrosive Chemicals Known to Induce RADS, Their K_{ow} Values, and Literature References

Chemical	K_{ow}	Reference
Uranium hexafluoride	0.21	[83]
Hydrazine	-1.47	[83]
Chlorine	-0.85	[83–87]
Glacial acetic acid	-0.17	[88]
Sulfur dioxide	-2.2.0	[84, 89]
Oxides of nitrogen	-0.58	[84]
Phosgene	-0.71	[85]
Hydrogen sulfide	-1.38	[84, 85, 90]
Hydrogen chloride	0.54	[84, 85]
Sulfuric acid	-2.20	[84, 85, 89, 90]
Chloroacetyl chloride	-0.22	[84]
Sodium fumes	-0.77	[84]
Phosphoric acid	-0.77	[85]
Sodium hydroxide ^a	-3.88	[86]
Ethylene oxide	-0.30	[87]
Calcium oxide	-0.57	[87]

^aCo-exposed with silicon tetrachloride ($K_{ow} = 1.77$) and trichlorosilane ($K_{ow} = 2.26$).

Since its first identification more than two decades ago, RADS has been studied by numerous researchers and clinicians. An analysis of the published material reveals that RADS is triggered by corrosive, irritating, and sensitizing chemicals. The onset of RADS following exposures to corrosives shows that single hydrophilic chemicals can be the causative agents. The onset of RADS following exposures to irritants, however, always requires that the exposures be to mixtures of hydrophiles and lipophiles [109]. Table 17.10 lists sensitizing chemicals known to induce RADS.

Table 17.11 Irritant Chemical Mixtures Known to Induce RADS, Their K_{ow} Values, and Literature References

	Mixture	K_{ow}	Reference
1	Decane	5.01	[83]
	Ethylbenzene	3.15	
	Toluene	2.78	
	Xylene	3.15	
	Epichlorohydrin	0.45	
2	Polyethoxylated vegetable oil	NA	[83]
	Dipropylene glycol	−0.64	
	Terpene hydrocarbon	4.83	
	Sodium nitrate	−4.39	
	Complex unsaturated aldehyde	NA	
3	Isobornyl acetate	3.86	[9]
	Phenol	1.46	
	Formaldehyde	0.35	
	Styrene	2.95	
	Methylene chloride	1.25	
	Methanol	−0.77	
	Aromatic and aliphatic hydrocarbons	3.0–4.0	
4	Mixture of aldehydes, ketones, hydrocarbons, alcohols, organic acids	−0.31 to 5.74	[91]
5	Epichlorohydrin	0.45	[89]
	Bis-phenol(a)	3.32	
	Methyl isobutyl methane	3.90	
	Ethylene glycol monobutyl ether	0.83	
	Mineral spirits	5.00 (est)	
6	Isobutane	2.76	[92]
	Ethyl acetate	0.73	
	<i>n</i> -Heptane	4.66	
	Fluoroaliphatics	0.75	
7	2,4-D	0.65	[91]
	MCP	3.13	
	Dicamba	1.13	
	Naphthalene	3.30	
	Solvent naphtha	5.00 (est)	
	Dinitroaniline	1.29	

NA, not available.

Table 17.11 lists irritant mixtures known to trigger RADS. Both tables are referenced to the literature. K_{ow} values are included in both tables to demonstrate hydrophilic or lipophilic nature. It should be noted that the terms corrosive and irritant as used here are those defined earlier in Section 17.1.

It should be noted that there have been two reports in the literature of RADS apparently being induced by exposures to bromotrifluoromethane (BTM) and

bromochlorodifluoromethane (BCDFM), fluorocarbons used in fire extinguishers [93, 94]. Both are irritant chemicals, and the effects noted seemingly contradict the observation made above that RADS induced by irritants is always to mixtures of lipophiles and hydrophiles. Both BTM and BCDFM, however, thermally decompose and hydrolyze to haloacids (HCl, HBr, and HF) and their corresponding carbonyl halides (carbonyl chloride, bromide, and fluoride), chemicals that are corrosive to human tissue. In the two studies reported, no analysis of the air inhaled by the injured individuals was carried out. It is strongly suspected that their injuries were due to the presence of corrosive decomposition products. This suspicion is supported by the widespread use of both BTM and BCDFM without other similar incidents being reported.

RADS, as described above, requires the onset of symptoms within 24 h of exposure to a high concentration of individual chemical or mixture. Some researchers have reported the onset of RADS following repeated low-dose exposures to respiratory irritants and have labeled the phenomenon low-dose RADS [50, 95]. Low-dose RADS apparently bridges the gap between RADS, caused by one-time exposure, and OA, caused by chronic exposures to affecting chemicals. These observations should not be surprising, since the chemicals known to induce OA and RADS are the very same species that differ only in concentrations of exposure. Low-level RADS causation may be considered as being due to middle-level exposures to such chemicals.

17.6 Respiratory Carcinogens

Much of the research into cancer of the respiratory system has been devoted to identifying lung carcinogens. Several chemical mixtures are known to increase lung cancer risk. These include tobacco smoke, which contain PAHs and cadmium, known as carcinogens; other mixtures containing PAHs; commercial oils; and mixtures of chemicals and radiation [108]. Illustrative examples of respiratory system carcinogenic chemical mixtures are as follows.

Workers in aluminum production, coal gasification, coke production, iron and steel foundries, tar distillation, shale oil extraction, wood impregnation, roofing, road paving, carbon black production, carbon electrode production, chimney sweeping, and calcium carbide production are all exposed to PAHs and are known to have increased rates of lung cancer relative to the general population [96, 97].

Metal machining, printing press operating, and cotton and jute spinning workers are also at higher risk for lung cancer than the general population [98]. These workers use mineral oils that are complex mixtures of aliphatic and aromatic hydrocarbons. The oils are formulated into end products containing a variety of additives and contaminants. These include nitrosamines, chlorinated hydrocarbons, sulfur, amines, and formaldehyde.

Workers who process uranium and those employed in atomic power laboratories also are at increased risk for lung cancer [99, 100]. These workers are typically exposed to complex mixtures of chemicals and radiation.

The complexities of the mixtures just described make it difficult to ascribe the increased lung cancer rates to any particular chemical or mixture. All the above exposures are to mixtures of lipophiles and hydrophiles, which have been shown to be associated with unexplained cancer clusters [101].

Though a small percentage of the lung cancers can be attributed to radon and asbestos exposure, almost all cases of this disease are associated with tobacco smoke inhalation. For the year 2000 it is estimated that 90–95% of all lung cancers in men and 74–85% of lung cancers in women in Europe and North America can be attributed to tobacco use [102]. The lower incidences for women are due to lower smoking rates in women than in men. As discussed in Chapter 15, 29 different carcinogens have been identified in tobacco smoke, a complex mixture containing more than 4000 different individual chemicals. This makes assigning a particular lung carcinogen the subject for ongoing research. It should be noted that lung cancer is virtually nonexistent in East and West Africa, where tobacco is not smoked [102].

17.7 Unanticipated Respiratory Effects of Chemical Mixtures

In keeping with the theme of this book, the unanticipated effects of respiratory exposures to chemical mixtures are examined here. As was seen in the previous sections, mixtures of irritants, as well as single sensitizing and corrosive chemicals, are known to produce respiratory effects in humans. The following are case studies from the literature which exemplify the respiratory toxicity of chemical mixtures. Each case is presented with a list of the chemicals involved, their octanol:water partition coefficients (K_{ow}), the effects observed following the exposures, and the literature reference (which immediately follows the case number). In all instances, the toxic effects observed were not predicted from considerations of the toxicities of the individual constituents and exposures were to mixtures of lipophiles and hydrophiles.

Case 1 [83]

A 19-year-old grocery clerk, who was previously in good health, developed cough dyspnea and other symptoms following his exposure to fumes from a concrete floor sealant used to coat a stockroom floor. He was subsequently diagnosed with RADS. The subject sealant contained the following chemicals:

Decane	5.01
Ethyl benzene	3.15
Toluene	2.73
Xylene	3.15
Epichlorohydrin	0.45

Though these chemicals are mild respiratory irritants, they are not individually known to produce the severe effects found in the subject individual.

Case 2 [14]

Woodworkers at a carpentry works facility were found to have reduced pulmonary function following their shifts compared to controls. Testing of the atmosphere in the workplace showed the presence of the following chemicals:

Formaldehyde	0.35
Terpene hydrocarbons	2.43–4.83
Dusts	

The formaldehyde and terpene levels were well below their TLVs and the dust levels were well within prescribed limits. At the levels measured, no respiratory effects are anticipated for the individual chemicals.

Case 3 [102]

Respiratory symptoms, including chest tightness, shortness of breath, and coughing, were reported for histology technicians as a result of their exposure to the following chemicals:

Formaldehyde	0.35
Chloroform	1.97
Toluene	2.73
Xylene	3.15
Ethanol	–0.31

All levels of exposure were below those to which respiratory symptoms could be attributed.

Case 4 [103]

Newspaper pressmen exposed to solvents and oils developed pulmonary and upper respiratory tract symptoms following their exposures. The chemicals they inhaled included:

D-Limonene	4.57
Various glycol ethers	0.83–1.14
Kerosene	5.00 (average value)
Aliphatic hydrocarbons	3.15–5.50
Isopropyl alcohol	0.05
Butyl carbitol	0.56

All exposures to these chemicals, as well as to various oils that were in use, were within PEL values and no respiratory symptoms were anticipated for any of the chemicals at the levels of exposure.

Case 5 [9]

Low levels of an applied herbicide/insecticide mix were drawn into the uptake air of a commercial building. Several workers in the building immediately reported respiratory symptoms (including dyspnea, chest tightness, and coughing). One individual was permanently injured and subsequently diagnosed with RADS. The chemical mixture to which the workers were exposed included:

2,4-D	0.65
MCPP	3.13
Dicamba	1.13
Solvent naphtha	3.0–5.5
Naphthalene	3.30
Dinitroaniline	1.29

All chemicals were present at values far below their TLVs and no respiratory effects were predicted from the known toxicologies of the individual species.

Case 6 [8]

In an effort to study SBS, 14 volunteers were exposed to a synthetic mixture of chemicals typically found in “sick buildings.” The chemicals contained in the mixture included:

<i>p</i> -Xylene	3.15
<i>n</i> -Butylacetate	1.78
<i>n</i> -Butanol	0.88
Ethyl benzene	3.15
<i>n</i> -Hexanal	1.78
1-Decene	5.12
1-Hexane	3.90
<i>n</i> -Nonane	4.76
<i>n</i> -Decane	5.01
α -Pinene	4.83
Ethoxyethylacetate	0.59
1,1-Dichloroethane	1.79
<i>n</i> -Undecane	5.74
Isopropanol	0.05
Cyclohexane	3.44
1,2,4-Trimethylbenzene	3.63
<i>n</i> -Propylbenzene	3.69
2-Butanone (MEK)	0.29
<i>n</i> -Pentanal	1.31
3-Methyl-2-butanone (MIPK)	0.84
4-Methyl-2-pentanone (MIBK)	1.31
1-Octane	5.18

All chemicals were at concentrations far below those considered to be respiratory hazards, yet respiratory responses were noted in the volunteers immediately upon exposure, 4 h later and 18 h later.

Case 7 [57]

A school custodian who had worked for 18 years developed symptoms of wheezing, cough, and chest tightness after removing graffiti from school walls, a chore he was frequently called upon to do. The removing products he used contained the following chemicals:

Dimethyl glutarate	0.90
Dimethyl adipate	1.39
γ -Butyrolactone	-0.31
Dimethyl succinate	0.40
Ethylene glycol <i>n</i> -butyl ether	0.83
Propylene glycol butyl ether	0.98
D-Limonene	4.57
Alkyl polyglycoside	NA
Propylene carbonate	0.08

The man's symptoms were significantly worse when he was assigned to graffiti removal and eased when he was away from the job. He remained symptomatic even after leaving the job. None of the individual chemicals in either of the two products are expected to produce the OA induced in this man.

Case 8 [89]

A group of 39 people reported respiratory symptoms (wheezing, chest tightness, difficulty breathing) within hours of exposure to a reformulated aerosol spray leather conditioner. The chemicals contained in the product included:

Isobutene	2.76
Ethyl acetate	0.73
<i>n</i> -Heptane	4.66
Fluoroaliphatics	0.75

Most of the individuals reported the onset of symptoms immediately after use, including some who had used the product outdoors. None of the individual chemicals in the product are known to cause the asthmatic symptoms that were observed.

Case 9 [91]

A computer operator developed RADS following his exposure to chemicals contained in an epoxy resin coating that was applied to a concrete floor in his presence.

The computer operator's coworker did not develop RADS, but developed a chronic cough. The coating product contained the following chemicals:

Epichlorohydrin	0.45
Bisphenol(a)	3.32
Polyamide resin	NA
Methyl isobutyl methane	3.21
Ethylene glycol monobutyl ether	0.83
Mineral spirits	3.00–5.00

None of the chemicals contained in the coating are known to cause asthma or RADS.

Case 10 [104]

Laboratory animals exposed to disposable diaper emissions have demonstrated pulmonary irritation upon inhalation of these emissions in a test chamber. Two brands of these diapers generated the following chemicals in the test chamber:

Brand 1

<i>m</i> -Xylene	3.15
<i>p</i> -Anisaldehyde	1.79
Ethylbenzene	3.15
Styrene	2.95
Cumene	3.66
Dipentene	4.57
<i>m</i> -Methoxybenzaldehyde	1.79
Methyl cinnamate	2.36

Brand 2

Toluene	2.73
1,3,5-Trimethylbenzene	3.42
TCE	2.42
1-Methylcyclopentylamine	1.79
Dipentene	4.57

Though exposure levels of all emissions were below their TLVs, these emission mixtures produced pulmonary irritations in mice.

Case 11 [9]

Shortly after installation of new carpeting in her home, a woman with no previously known respiratory ailments experienced dyspnea, chest tightness, and difficulty

breathing. Testing of the air in the home revealed that chemicals associated with new carpet emissions were present. The chemicals identified included:

BHT	5.10
Formaldehyde	0.35
Styrene	2.95
2-Butoxyethanol	0.83
Undecane	5.74
Acetic acid	-0.17
Octanal	2.78
Dipropylene glycol	-0.64
2-Phenoxyethanol	1.16
2-(2-Butoxyethoxy)-ethanol	0.56
Naphthalene	3.30
Decane	5.01
Dichlorodifluoromethane	2.16
Isobutene	2.76
Propane	2.36
<i>n</i> -Butane	2.89
Ethanol	-0.31
Acetone	-0.24
Trichlorofluoromethane	2.53
Isopropanol	0.05
Toluene	2.73
Hexanal	1.78
Benzaldehyde	1.48
α -Pinene	4.83
D-Limonene	4.57

The concentrations of all species, as well as for total VOCs, were well below levels considered harmful to humans.

Case 12 [82]

A housewife who had previously been completely asymptomatic and with no respiratory symptom history began wheezing within minutes after a fumigating mixture of chemicals was applied to her kitchen following a fire. The mixture contained:

Vegetable oil	NA
Dipropylene glycol	-0.64
A terpene hydrocarbon	4.64 (est)
An unsaturated aldehyde	1.78-2.78 (est)
Isobornyl acetate	3.86
Sodium nitrate	-0.79

The woman was subsequently diagnosed with RADS following her exposure to this mixture of irritants.

Case 13 [9]

A 56-year-old purchaser of a new yacht reported the onset of dyspnea, tightness of chest, and cough whenever she was in the closed cabin of the yacht. Within 3 months she developed permanent asthma. The chemicals contained in the yacht cabin air included:

Toluene	2.73
Formaldehyde	0.35
Benzene	2.13

The concentrations of all three air contaminants were below those known to produce respiratory symptoms and cause OA.

Case 14 [105]

Biomass fuels (wood, coal, etc.) are used by more than 2 billion people worldwide for cooking and home heating. Burning of such fuels produces mixtures of toxic gases and particles that are the most widespread source of indoor air pollution. A recent study in rural Mexico has shown that the introduction of more efficiently burning biomass stoves significantly reduced the incidence of respiratory symptoms and improved lung function among those using such stoves [105].

The case studies just described are representative of many others to be found in the literature for instances where low-level mixtures of lipophiles and hydrophiles act together to induce respiratory effects that are not anticipated from the levels of exposure.

Not all mixtures that are toxic to the respiratory system are mixtures of lipophiles and hydrophiles. In some instances, irritant chemicals react to produce more toxic species. Chloramine-induced pneumonitis from the mixing of household ammonia and bleach is an example of this phenomenon [106, 107]. Household ammonia cleaner is usually a 5–10% aqueous solution of ammonia. Household bleach is generally a 5.25% solution of sodium hypochlorite. At these concentrations, these chemicals alone act as respiratory irritants. When mixed together, however, they react to form monochloroamine, dichloroamine, and trichloroamine, as shown in Figure 17.1. Chloramines are far more toxic than either hypochlorite or ammonia and are capable of producing inflammation and edema of the respiratory system. Case 12 is an example of the toxicity of chloramines.

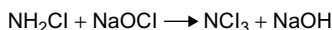
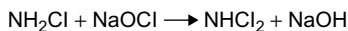
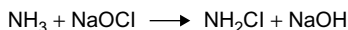


Figure 17.1 Reaction of ammonia and sodium hypochlorite to produce chloramines.

Case 15 [107]

A 62-year-old woman was without respiratory illness until the day she cleaned with a mixture of ammonia and bleach. She noted eye, nose, and throat irritation, but continued to clean for several hours. Several hours later, she noted increasing respiratory distress and called an ambulance. Upon arrival, paramedics had to intubate her at home due to respiratory failure. The woman recovered after 30 days of hospitalization, though a roentgenogram taken 38 days after admission showed residual interstitial infiltrate.

17.8 Summary

The continuing worldwide increase in respiratory disease corresponds to increases in the release of chemicals into the atmosphere. Respiratory irritation, sensitization, asthma, RADS, and lung cancer can be attributed to numerous single chemicals whose toxicological properties are, for the most part, well known. Many unexplained incidences of respiratory disease cannot be attributed to single chemical exposures, but have been shown to occur when exposures are to chemical mixtures that are composed of at least one lipophile and one hydrophile. The sources of such mixtures include diesel exhausts, tobacco smoke, carpet emissions, paint fumes, and cleaning products. Prevention of chemically induced respiratory diseases should include limiting exposures to these chemical mixtures.

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18 Nervous System

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18.1 Introduction

The nervous system is comprised of the brain, spinal cord, sensory organs, and a vast array of nerves that control thought, movement, heart function, respiration, vision, hearing, speech, smell, touch, and many other physiological functions. The nervous system is readily attacked by toxic chemicals for the following reasons:

1. Nerve cells, unlike other body cells, normally do not regenerate once killed. Accordingly, toxic damage to the brain or spinal cord is usually permanent.
2. The structure of nerve cells is remarkably different from that of other body cells (see Figure 18.1). The much greater surface area of nerve cells leaves them more vulnerable to chemical attack.
3. Nerve cell loss and other irreversible nervous system declines generally increase as the body ages. Toxic actions on the nervous system can, therefore, profoundly affect the body as it ages.
4. Seemingly minor alterations in the structure or function of the nervous system can have major impacts on neurological, behavioral, or physiological body functions.
5. Many neurotoxic chemicals easily cross the blood–brain barrier, leading to direct exposure of brain regions to toxic chemicals carried in the blood.
6. Unlike other tissues, the brain is composed of 55% fat tissue. This makes the brain a ready depository for toxic lipophilic chemicals and the hydrophilic chemicals dissolved in them.
7. Myelin has the highest lipid content, 75%, of all biological membranes. This facilitates the absorption of lipophilic chemicals that can lead to serious nervous system injury.
8. Numerous chemicals can interfere with the delicate electrochemical balance necessary for nervous system communication of vital body information.

Neurotoxicity is defined as an adverse effect upon the structure or function of the nervous system following exposure to a chemical agent. Conversely, a neurotoxic

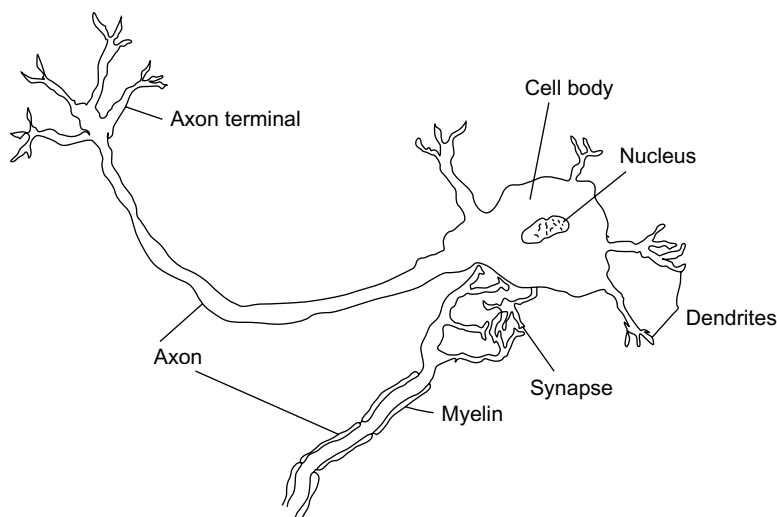


Figure 18.1 Structure of the nerve cell.

chemical is one that adversely affects the nervous system. The action of a neurotoxin can be at the cellular or molecular level. At the cellular level, a neurotoxin might, for example, affect the flow of sodium or potassium ions across the cell membrane, thereby disrupting the transmission of information between nerve cells. At the molecular level, it might interfere with protein synthesis in nerve cells, resulting in a reduced production of a neurotransmitter and a brain dysfunction. Toxic chemicals can cause a slow degeneration of the nerve cell body or axon, which may result in permanent neuronal damage [1].

Effects observed in humans following neurotoxic exposure include modification of motor and sensory activities, emotional states, integrative capabilities such as learning and memory, adverse effects on sensory systems (including sight, hearing, smell, touch, and pain sensation), behavior modification, sleep loss, speech impairment, delirium, hallucinations, convulsions, and death [1–4].

Neurotoxic chemical exposure to the fetus and young child may cause adverse developmental neurotoxic effects. These effects are the subject of the next chapter and will not be considered in detail here.

In keeping with the purpose of this book, the discussion of the neurotoxic effects of single chemicals will serve only as an introduction to the discussion of the neurotoxic effects of chemical mixtures.

18.2 Neurotoxic Chemicals

Numerous neurotoxic chemicals have been identified. These include pesticides (particularly, but not limited to, organophosphates and carbamates), aliphatic and aromatic hydrocarbons, alcohols, ethers, ketones, heavy metals (including lead, mercury, manganese, and others), and mixtures of these. Hundreds of individual chemicals are established or suspected neurotoxins [132]. The EPA Guidelines for Neurotoxicity Risk Assessment [4] and the Scorecard list of neurotoxicants [5] contain partial lists of neurotoxic chemicals. The actual number of chemicals with neurotoxic potential has been estimated to range between 3% and 28% of all of the approximately 80,000 chemicals in use (2400–22,400) [1]. Clearly, the number of mixtures possible is infinite, though little attention has been devoted to the neurotoxic effects of mixtures.

Organophosphate and carbonate pesticides act by inhibiting the AChE that hydrolyzes acetylcholine, a neurotransmitter. This inhibition in the CNS or peripheral nervous system prolongs the action at the neuron's synaptic receptors and produces clinically measurable overstimulation symptoms that include muscle weakness, perspiration, tremor, blurred vision, and salivation [6]. More than 90 different organophosphate pesticides have been identified [7].

Organochlorine pesticides act by exciting the nervous system and produce symptoms that include dizziness, headache, disorientation, confusion, loss of balance, weakness, muscle twitching, tremors, convulsions, and, in the extreme, coma [7].

Pyrethroids, though far less toxic to humans than to insects, induce repeated firing of nerve cells and cause incoordination, tremor, salivation, and irritability to sound and touch [7].

Table 18.1 Neurotoxic Pesticides

Organophosphates	Dieldrin
Azinphos-methyl	Toxaphene
Dichlorvos	Mirex
Tetraethyl pyrophosphate	Endrin
Ethyl parathion	Lindane
Diazinon	Heptachlor
Ethion	Chlordane
Chlorpyrifos	Pyrethroids
Malathion	Bathrin
Endothion	Tetramethrin
Chlorthiophos	Cyfluthrin
Thiometon	Fluvalinate
Carbamates	Resmethrin
Aldicarb	Chlorophenoxy Compounds
Propoxur	2,4-D
Dimetan	2,4,5-T
Bendiocarb	MCPA
Carbaryl	2,4,5-Trichlorophenoxypropionic acid (Silvex)
Organochlorines	
DDT	
Aldrin	

Chlorophenoxy herbicides are, by themselves, of relative low toxicity to humans. They are, however, often contaminated with dioxins, of which, 2,3,7,8-tetrachloro-p-dioxin (TCDD) is the most toxic, causing CNS and peripheral nervous system neuropathies [8].

A partial list of widely used neurotoxic pesticides is contained in Table 18.1. A complete list may be found in the literature [1, 7].

Volatile organic solvents that are commonly used in adhesives, paints, and cleaners, including aromatic hydrocarbons, halogenated hydrocarbons, ketones, ethers, and alcohols, act as depressants. Exposure to these can result in motor impairment, behavioral changes, and adverse effects on sensory perception [2]. Table 18.2 contains a partial list of neurotoxic volatile organic chemicals.

Heavy metal exposures can adversely affect those exposed in several ways. Even at relatively low levels, lead exposure can cause neurobehavioral problems including learning disorders [9]. Mercury compounds are powerful neurotoxins whose exposure leads to speech and vision impairment, a lack of coordination and severe developmental neurotoxic effects. MeHg is a potent neurotoxin. In one unfortunate incident in the mid-1950s, a chemical plant in Japan discharged MeHg into Minamata Bay. When local residents ate fish and shellfish which were contaminated with the MeHg, severe neurotoxic and developmental neurotoxic effects resulted in adults and their offspring

Table 18.2 Partial List of Neurotoxic Volatile Organic Chemicals

Aliphatic Hydrocarbons	Ketones
<i>n</i> -Hexane	Acetone
Isomethylhexane	MEK
Propane	Methyl- <i>n</i> -butyl ketone
Butane	MIBK
<i>n</i> -Heptane	Methyl- <i>n</i> -amyl ketone
Aromatic Hydrocarbons	Halogenated Compounds
Toluene	Methylene chloride
Xylene	Chloroform
Styrene	1,1,1-Trichloroethane
Alcohols	TCE
Methanol	PCE
Ethanol	Chlorodifluoromethane
<i>n</i> -Butanol	Dichlorodifluoromethane
Ethers	Trichlorofluoromethane
2-Butoxyethanol	Esters
Diethyl ether	Ethyl acetate
	<i>n</i> -Butyl acetate

[10, 11]. Another infamous MeHg poisoning occurred in Iraq in 1971 when wheat treated with it was consumed by large numbers of people. It is estimated that more than 50,000 individuals were affected and that some 5000 people died as a result of the consumption of the contaminated wheat [12].

Chronic exposure to low levels of mercury can also result in neurotoxic effects, as evidenced by the increased neurological symptoms observed in workers in a mercury thermometer manufacturing plant [13]. A good discussion of the toxicity of mercury is presented in a paper by Magos and Clarkson [14].

Manganese is an essential trace element in the human diet. Overexposure, however, can lead to numerous neurological effects including hallucinations, abhorrent behavior, emotional instability, and Parkinsonism [15].

Lead is highly toxic to the human nervous system. Even in low concentrations, it can cause neurobehavioral problems, including learning disorders in children [9].

Other neurotoxic metals include aluminum [16, 17], cadmium [18, 19], and thallium [20, 21].

18.3 Indicators and Symptoms of Neurotoxic Poisoning

Neurotoxic poisoning can result in five different categories of indicators. These and their symptoms are presented in Table 18.3. The material presented in this table and the format has been adapted from the literature [1, 4, 22].

Table 18.3 Indicators of Neurotoxic Poisoning and Their Symptoms**1. Structural or Neuropathological**

Gross changes in morphology, including brain weight

Histologic changes in neurons or glia (neuropathy, axonopathy, myelinopathy)

2. Neurochemical

Changes in synthesis, release, uptake of vital molecular species and/or neurotransmitter degradation

Changes in second-messenger-associated signal transduction

Changes in membrane-bound enzymes regulating neuronal activity

Inhibition and aging of neuropathy enzymes

Increases in glial fibrillary acidic protein in adults

3. Neurophysiological

Change in velocity, amplitude, or refractory period of nerve conduction

Change in latency or amplitude or sensory-evoked potential

Change in electroencephalographic pattern

4. Behavioral and Neurological

Changes in touch, vision (including color perception loss), auditory, taste, or smell sensations

Speech impairment

Changes in equilibrium

Pain disorders

Increased or decreased motor activity

Abnormal movement

Changes in motor coordination, weakness, twitching, paralysis, tremor, or posture

Decreased occurrence or absence, magnitude or latency of sensorimotor reflex

Changed magnitude of neurological measurement, including grip strength and hindlimb splay

Loss of coordination and unsteadiness

Seizures and convulsions

Changes in rate or pattern of activities

Changes in learning, memory, or attention span

Confusion

Sleep disturbances

Headache

Loss of appetite

Excitability

Depression

Irritability

Restlessness

Nervousness

Tension

Depression

Stupor

Fatigue

Delirium and hallucinations

5. Developmental

Changes in the time of appearance or lack of expected behavior elements during development, or failure to develop as expected

Onset of unexpected behavior patterns during development

Changes in growth or organization of nervous system elements

18.4 Mechanisms of Neurotoxic Action

A detailed treatment of the mechanisms by which neurotoxic chemicals act is beyond the scope of this book. The following discussion briefly addresses the subject. For greater depth, the reader is referred to the literature [23–26].

Neurotoxic chemicals enter the body via inhalation, ingestion, and/or dermal absorption. These chemicals and their metabolites enter the bloodstream and are partitioned from there into body tissues. Many neurotoxins are lipophiles and accumulate in adipose tissue. The brain is particularly vulnerable to lipophilic chemical attack since 50% of the dry weight of the brain is lipid, compared to 6–20% lipid makeup for other body organs. Not all neurotoxins, however, are lipophiles. Lead compounds, for example, which are hydrophilic, are potent neurotoxins.

Neurotoxicity cannot be explained by a single mechanism. Lipid-soluble molecules rapidly pass the blood–brain barrier and depress nerve cell membrane functions [23]. Carbon monoxide is a neurotoxin that acts by reducing oxygen supply to nervous system cells via inhibition of mitochondrial respiration [23]. OS has been implicated as the factor responsible for neurotoxic damage caused by various metals, including MeHg [27, 28]. Organophosphate and carbamate pesticides poison people by phosphorylation of the AChE at nerve endings [6, 7]. The enhanced neurotoxicity observed in those exposed to a mixture of *n*-hexane and methyl-*n*-butyl ketone is believed to be caused by a common metabolite, 2,5-hexanedione [29].

The mechanisms by which many neurotoxic chemicals and chemical mixtures act remain unknown. Much of the knowledge regarding the actions of chemical neurotoxins has been learned by empirical observation and epidemiological studies.

18.5 Neurodegenerative Diseases and Toxic Chemical Exposures

Neurodegenerative diseases (NDDs) are those in which the irreversible deterioration of neurons affects movement and/or memory. A number of these diseases have been associated with neurotoxic chemical exposures. These include Parkinson's disease (PD), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS, also called motor neuron disease, MND), and multiple sclerosis (MS). NDDs and their associations with neurotoxic exposures are introduced here. Specific examples and case studies are discussed in the following sections.

18.5.1 Parkinson's Disease

PD is a slowly progressing degenerative condition in which dopamine-producing cells in the brain are lost. Symptoms include tremor or trembling of the arms, legs, jaw, and face, slowness of movement, unstable posture, stiffness or rigidity of the limbs and trunk, and/or impaired balance and coordination. PD is slowly progressive and is related to an individual's genetic susceptibility, age, and environmental exposure over one's lifetime [30].

Insight into the environmental causes of PD was obtained in the 1980s when it was shown that an impurity in synthetic heroin, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP), a substance chemically similar to several pesticides, caused severe Parkinsonism in addicts who used this drug intravenously [31, 32]. It has been subsequently shown that exposures to pesticides [32–34], some heavy metals [35, 36], and volatile organic solvents [37–39] have resulted in increased incidences of PD.

Welding without proper protection from its fumes has been associated with PD as well as with multifocal myoclonus, mild cognitive impairment, and vestibular auditory dysfunction [40].

18.5.2 Alzheimer's Disease

AD is an NDD associated with loss of function and death of nerve cells in the brain. It is characterized by a progressive loss of mental function (dementia) with disorientation, confusion, and loss of memory and learning ability.

In some studies, increased incidences of AD have been associated with exposures to volatile organic solvents. These include aromatic hydrocarbons, alcohols, phenols, ketones, and other solvents [41, 42]. Other studies, however, have found no association between exposures to solvents and the onset of AD [43, 44]. Aluminum, cadmium, cobalt, dioxins, and other chemicals known to trigger formation of ROS have also been suggested as environmental causative agents for AD [45–49]. Heavy smoking in midlife, too, has been suggested as a cause of Alzheimer's Disease [133].

18.5.3 Amyotrophic Lateral Sclerosis

ALS, also known as MND and Lou Gehrig's disease, is the most common of a group of disorders in which neurons in the spinal cord and brain stem deteriorate and die, resulting in weakness and muscle deterioration.

Some studies have associated ALS with exposures to solvents [50, 51], 60Hz magnetic fields, and welding [52], while others have questioned these associations [53–55]. A study of twins, however, strongly suggested an association between exposures to solvent chemicals and ALS [56]. As of this writing, the connection between neurotoxic chemical exposure and ALS remains suggestive, but not definitively proven.

18.5.4 Multiple Sclerosis

MS is a CNS disorder in which myelin is gradually destroyed in patches throughout the brain or spinal cord, or both. This loss of myelin interferes with nerve transmissions and leads to muscular weakness, loss of coordination, numbness, tremors, and speech and vision disturbances. MS is thought to be an autoimmune disease.

MS has been associated with solvent exposures. Shoe and leather workers, who are exposed to numerous hydrocarbon- and ketone-containing glues, were observed to have an almost fivefold greater risk for MS than the general population [57]. Other studies showed an increased risk for MS in those who are occupationally exposed to solvents, ionizing radiation, and welding fumes, as well as for those who were in contact with animals [58, 59]. Epidemiological studies have also shown an association

between exposure to organic solvents and increased risk for MS [60, 61]. It should be noted, however, that other studies have not supported the connection between chemical exposures and MS [62, 63]. Here, too, the suggestive evidence for the connection to neurotoxic exposure and increased risk for contracting MS is strong, but not definitive.

18.6 Neurotoxicity of Chemical Mixtures

Virtually all human environmental exposures to toxic chemicals are to mixtures. This is particularly the case for exposures to pesticides, heavy metals, and organic solvents, known as neurotoxins. Despite this, relatively few studies have been carried out on the neurotoxic effects of chemical mixtures. This section addresses the results of these mixture studies.

As discussed in Section 18.3, neurotoxic chemicals act via multiple mechanisms. One explanation offered as to why some mixtures of neurotoxins produce enhanced effects is based on a multi-hit hypothesis [64]. This hypothesis argues that while the brain may compensate for the effects of a single chemical acting on a particular target in it, the brain cannot as effectively respond to a multi-target attack via multiple attack mechanisms. When one couples this approach with the greater absorption of neurotoxins when exposures are to mixtures of lipophiles and hydrophiles [65], it becomes clear that effects produced by exposures to mixtures can be far different from those predicted from considerations of single chemicals only. It has also been shown that lipophilic species facilitate the absorption of hydrophilic ones, resulting in the absorption of greater quantities of hydrophiles than expected [65].

Mixtures of pesticides, heavy metals, or organic solvents often produce unanticipated neurotoxic effects. The following are published examples of such effects. Octanol:water partition coefficients (K_{ow}) are given for all chemicals cited to demonstrate lipophilicity or hydrophilicity.

18.6.1 Pesticide Mixtures

In a study on laboratory animals, it was shown that a mixture of five organophosphate pesticides produced greater than additive neurotoxic effects [66]. The five pesticides were:

Chlorpyrifos	4.66
Diazinon	3.81
Dimethoate	0.78
Acephate	-0.85
Malathion	2.36

As can be seen, even though all the pesticides are organophosphates, they vary widely in K_{ow} . It is hypothesized that the lipophilic species (chlorpyrifos, diazinon,

and malathion) facilitate the absorption of the hydrophilic species (dimethoate and acephate) and thereby multiply the neurotoxic effects.

Pyrethroids are ion channel toxins that prolong neuronal excitation [67]. Despite their lipophilic character, pyrethroids are slowly absorbed through the skin and have limited toxicities. When applied with organophosphates, however, the organophosphates enhance pyrethroid neurotoxicity [68]. It is hypothesized that here too, the lipophilic species acts as a carrier of the hydrophilic species, resulting in greater uptake of pyrethroids than would occur in the absence of a lipophilic species.

Military personnel in the first Gulf War (1991) were deliberately exposed to a combination of three chemicals to protect their health. The three chemicals were: PB, an anti-nerve agent; DEET, an insect repellent; and permethrin, an insecticide. Of the three quarters of a million personnel who served in the war, approximately 30,000 complained of neurological symptoms. PB is considered to be safe to humans in the doses administered. It is a quaternary dimethyl carbamate that is used as a treatment for myasthenia gravis at higher doses than those administered to military personnel. DEET has been used extensively by humans as an insect repellent. Symptoms associated with DEET poisoning include tremors, seizures, speech impairment, and restlessness. High levels of DEET have been shown to produce demyelination. It is not known to be toxic at the levels used by military personnel. Permethrin is a synthetic pyrethroid insecticide that affects sodium channels and leads to prolonged depolarization and repetitive discharges in presynaptic nerve fibers that are associated with tremor, hyperactivity, and convulsions. It, too, however is not believed to be toxic at the levels applied to soldiers [69].

The three chemicals vary widely in lipophilicity/hydrophilicity, with K_{ow} values that range from -3.73 to 7.74 :

PB	-3.73
DEET	2.18
Permethrin	7.74

In a series of experiments on laboratory animals (hens and rats) it was shown that treatment with each of the three compounds alone had minimal toxicity. All binary combinations, however, produced greater neurotoxicity than the individual compounds and a mixture of all three showed further enhanced neurotoxic effects. The effects noted included locomotor dysfunction, tremor, and behavioral effects [69–71]. Since the laboratory effects observed mirror those seen in Gulf War veterans, the authors of these studies suggest that the veterans could have been poisoned by the mixture to which they were exposed.

Maneb ($K_{ow} = 0.62$), a dithiocarbonate, and paraquat ($K_{ow} = -2.71$), an organophosphate, show potentiated neurotoxic effects in animal studies when co-exposure to these occurs during gestation. These pesticides also demonstrate both progressive and cumulative neurotoxicity, including marked vulnerability to the effects of paraquat following gestational exposure to maneb [64].

The amines, spermidine, spermine, and putrescine, which are all hydrophiles, act synergistically with malathion, a lipophile, to inhibit cholinesterase activity in toads.

Spermidine	-0.66
Spermine	-0.68
Putrescine	-0.70
Malathion	2.36

Spermidine plus malathion application resulted in a 13-fold increase in toad larvae mortality, while spermidine alone had no effect on the enzyme [72].

It has been shown that co-exposure to the pesticide tributyltin ($K_{ow} = 7.35$) and the PCB 126 isomer ($K_{ow} = 6.98$) results in potentiated neurotoxicity [73]. Both of these pesticides are lipophiles and the mechanism behind the potentiated effect of the mixture is unknown.

As discussed earlier, MPTP has been shown to be causal in the development of PD. The structural similarity between MPTP and organophosphate pesticides suggests that such pesticides might also cause PD, and epidemiological studies have demonstrated such relationships [33]. In an in vitro study, it was demonstrated that coadministration to the organophosphate endosulfan ($K_{ow} = 3.83$) and the dithiocarbamate zineb ($K_{ow} = -0.39$) results in synergistic apoptotic/necrotic process action in human neuroblastoma cells. The authors concluded that such pesticide-induced neuronal cell death may be associated with early and late apoptosis of dopaminergic neurons and be causal for PD [74]. This study collaborates an earlier one in which the combination of paraquat and maneb (also a dithiocarbamate) had a greater impact on the dopamine system of mice than either compound administered alone. The mixture, but not paraquat alone, reduced motor activity immediately after treatment. In this study too, the authors conclude that the synergistic effects of paraquat and maneb suggest that such mixtures could play a role in the etiology of PD [75].

The effects of pesticide chemical mixtures on NDDs other than PD have not been studied to date. It should not be surprising if relationships are established in the future.

The neurotoxic effects of pesticide mixtures are not limited to acute exposures. Chronic low-level exposures over many years of agricultural work or other pesticide handling have been shown to produce deficits in neurological performance. Such deficits have been observed for those exposed to carbamate as well as organophosphate pesticides [76–78]. Banana workers exposed to low levels of organophosphate and carbamate pesticides in the long term were observed to score lower on tests measuring psychomotor and visuomotor skills and language function [76]. Neurobehavioral performances of Hispanic immigrant workers who were chronically exposed to low levels of organophosphate pesticides tested with lower neurobehavioral performances than those in a non-agricultural Hispanic immigrant population [77]. As discussed in Chapter 14, agricultural pesticides are often applied as mixtures and commercial pesticides are dissolved or suspended in solvents, surfactants, and other processing chemicals. Accordingly, it is most likely that the individuals observed in the studies just cited were exposed to mixtures composed of multiple lipophilic and hydrophilic species.

18.6.2 Organic Solvent Mixtures

As discussed in Section 18.2, many organic compounds are neurotoxic. Numerous studies have shown that exposures to low levels of organic solvent mixtures induce a wide variety of neurotoxic symptoms. Regrettably, many of the studies that address the neurotoxic effects of organic solvent mixtures fail to identify the mixture components or, when doing so, do not provide quantitative exposure data. Often, however, the compositions and approximate concentrations can be inferred from the work that the exposed individuals were doing and the settings in which they were working. When analyzed this way, it becomes clear that there are many instances of neurotoxic impact from low-level exposures of lipophile/hydrophile mixtures [3, 79–83]. These studies also demonstrate that neurotoxic effects are not limited to short-term acute exposures, but may also ensue following long-term chronic exposures [80, 84]. It has also been shown by pharmacokinetic models that exposures to the same mixtures under resting and working conditions result in far greater uptake of organic solvent mixtures when a person is working relative to when resting [85].

Some neurotoxic effects of exposures to organic solvent mixtures are not anticipated. Solvent mixture exposures to lipophilic/hydrophilic mixtures have been shown to impair color vision in those exposed to paints and lacquers, printers, and workers in microelectronics plants [86–88]. The authors of these studies did not offer any hypothesis for the observed effects.

Moderate hearing losses have been noted in workers exposed to organic solvents [89]. Synergistic hearing loss effects have been reported in workers jointly exposed to noise and solvents, both within occupational exposure limits [90]. No mechanistic explanations have been offered for these ototoxic effects.

Much qualitative and quantitative information about the neurotoxic effects of exposures to organic solvents has been gathered from studies on painters [91–100]. Solvent-based paints typically contain aliphatic and aromatic hydrocarbons, alcohols, ketones, and esters. A partial but representative list of these and their K_{ow} values are given in Table 18.4. As can be seen from this list, a number of lipophilic and hydrophilic chemicals are present in almost all paints.

Table 18.4 Organic Solvents Typically Found in Solvent-Based Paints and Their K_{ow} Values

Toluene	2.73
Xylene	3.15
C ₆ to C ₉ aliphatic hydrocarbons	4.10–6.15
Isopropanol	0.05
<i>n</i> -Butanol	0.88
Acetone	–0.24
MIBK	1.19
Ethyl acetate	0.73
<i>n</i> -Butyl acetate	1.78

The quantities of solvents in paints vary with desired characteristics (e.g., drying time desired) and application (building interiors, automotive surfaces, and architectural applications). Other solvents, including chlorinated hydrocarbons and terpenes, are also formulated into paints. Virtually all solvent-based paints contain mixtures of lipophiles and hydrophiles. The exposures of painters to low levels of solvents (sufficiently low enough so that they do not experience acute symptoms at the time of exposure and below the TLVs for the individual solvent molecules) enable one to ascribe neurotoxicological reactions to low-level mixture exposures.

The neurological health of painters has been extensively studied. Painters have been found to suffer from impaired behavioral effects [91, 92, 98], sensory and sensorimotor neuropathies [94], psychiatric function [95, 96, 99], and learning and memory deficiency [97] problems. In the studies just cited, as well as many other similar ones, exposures were generally of low level, occurred over a period of years, and were to mixtures of lipophilic and hydrophilic chemicals. Other studies on exposures to single chemicals have established safe exposure levels for single chemical species. The evidence gathered from painters' exposures shows that low-level exposures to lipophilic/hydrophilic mixtures are associated with neurotoxic effects not predicted from considerations of the neurotoxicities of the single species.

Low-molecular-weight ketones are not, by themselves, particularly neurotoxic. They do, however, potentiate the neurotoxicities of alkanes and other compounds [29, 101–108]. The neurotoxic synergism of *n*-hexane and methyl-*n*-butyl ketone has long been known and is generally attributed to their common metabolite 2,5-hexanedione [29, 105]. Synergism, however, has also been reported for mixtures of *n*-hexane and MIBK [101, 102] as well as for *n*-hexane and MEK [103–105]. The potentiated effects of ketones on alkanes are not limited to *n*-hexane. Peripheral neurotoxicity in a shoemaker was reported following his exposure to a mixture of MEK, ethyl acetate, cyclohexane, and *n*-heptane [106]. The mechanism(s) for these synergistic effects are as yet unknown.

O-Ethyl *O*-4-nitrophenyl phenylphosphonothionate (EPN) is a cholinesterase inhibitor. Combined exposure to both EPN and methyl-*n*-butyl ketone resulted in a neurotoxic effect in hens that was twice that expected from an additive effect of the two chemicals [107] and treatment of hens with a combination of EPN, MIBK, and *n*-hexane produced acute cholinergic and delayed neurotoxic symptoms [108].

Inhalation of volatile organic solvents can produce acute depressant effects and even death in humans when inhalation is concurrent with exposure to other depressants. For example, combined ingestion of ethanol and inhalation of carbon tetrachloride or TCE produces enhanced depressant effects and toluene and 1,1,1-trichloroethane enhance the effects of CNS depressant drugs [2].

Histology technicians exposed to formaldehyde ($K_{ow} = 0.35$) and xylene ($K_{ow} = 3.15$) or toluene ($K_{ow} = 2.73$) exhibit symptoms of neurobehavioral impairment of memory, judgment, and equilibrium [109]. These effects cannot be attributed to the individual chemicals in the mixtures.

Hydrocarbon fuels are complex mixtures of more than 250 different molecular species. Compounds contained in such fuels include benzene, toluene, xylene, various alkyl benzenes, naphthalene, hexanes, heptanes, octanes, and higher molecular weight

alkanes, all of which are neurotoxic. Fuel additives further complicate the mixtures. Acute and chronic exposures to low levels of hydrocarbon fuels, including gasoline, kerosene, diesel fuel, and jet fuel, result in neurotoxic and neurobehavioral effects that are at times seemingly different from those anticipated from exposure to the individual chemicals [110].

Many household products contain neurotoxic chemical mixtures. These include fragrance products [111], marking pens [112], and air fresheners [113]. These products contain mixtures of lipophilic and hydrophilic chemicals and exposures in home use are typically far below the TLVs of any of the individual chemicals. Exposures to these products, however, in test chambers produce unpredicted behavioral abnormalities in laboratory animals including altered gait, loss of balance, hypoactivity, tremors, and other symptoms. Though no specific human neurotoxic effects have been noted, these studies suggest that neurotoxic impacts on people are likely.

Many household and commercial neurotoxic products are intentionally inhaled for recreational purposes. The volatile solvents contained in these products are rapidly absorbed and carried to the brain, producing a feeling of euphoria. The practice, also known as glue sniffing or huffing, is widespread among adolescents and has resulted in numerous permanent neurological injuries and deaths when excessive quantities of neurotoxic solvents have been absorbed [114, 115]. Table 18.5 lists volatile chemicals that are frequently abused by intentional inhalation and the products which contain these compounds.

Frequently, the intentionally inhaled chemicals are mixtures, as is the case when paints and adhesives are abused. Since the intent of those inhaling these chemicals is to get as much as possible per inhalation, the quantities of single chemicals and mixtures absorbed are often far above PELs and produce acute poisonings [115].

Table 18.5 Volatile Chemicals Frequently Abused by Intentional Inhalation and Products Containing These Compounds

Chemical	Product
Acetone	Nail polish removers, adhesives
Aliphatic and aromatic hydrocarbons	Gasoline, lighter fluids, paints, paint thinners
BCDFM	Fire extinguishers
Butanes	LPG fuel, cigarette lighters
2-Butanone (MEK)	Adhesives, pipe cements
Chlorofluoromethanes	Aerosol propellants
Ethyl acetate	Adhesives
MIBK	Paints, adhesives
Methylene chloride	Paint strippers
Propane	Heating and cooking fuels
Tetrachloroethylene	Dry-cleaning fluid, spot removers
1,1,1-Trichloroethane	Degreasers, typewriter correction fluids, fabric stain-proofing products
Toluene	Adhesives, paint products
Xylene	Adhesives

In instances I have investigated and observed deaths and brain damage to the point where the individuals were left in permanent vegetative states.

Tourette syndrome (TS) is a disorder characterized by waxing and waning motor and vocal tics. It has been known for some time that the frequency and intensity of tics in those with TS are promoted by stress and anxiety. Recently, however, it was shown that caffeine- and thein-containing drinks, preservatives used in food, refined sugar, and synthetic sweeteners increase tics in TS patients [116]. The chemical compositions of these tic promoters suggest that other organic compounds may also act this way. Research is ongoing in this area.

18.7 Case Studies: Neurotoxic Chemical Mixtures

The case studies presented here are all from the published literature. In every study the neurotoxic effects found are related to exposures to chemical mixtures of lipophiles and hydrophiles that induced neurotoxic effects not anticipated from the individual chemicals. The K_{ow} values for each of the chemicals are given. If not listed in a column, they follow the individual chemical names in parentheses.

Case 1 [117]

Encephalopathy is a term for any diffuse disease of the brain that alters brain function or structure. A 57-year-old man who had spent 41 years as a painter was disabled and forced to retire. He was diagnosed with chronic toxic encephalopathy. The man started work as a painter at age 16. He started experiencing impaired short-term memory function while in his forties. His condition progressed until after he retired and his exposures to the paint solvents ceased. Following his retirement, his condition stabilized and even improved in some areas. Material safety data sheets provided by his employer indicated that this man had been exposed to lead, titanium dioxide, creosote, and the following volatile solvents:

Ammonia	-1.38
Chlorine	0.85
Methanol	-0.77
Isopropanol	0.05
MEK	0.29
MIBK	1.19
Formaldehyde	0.35
Carbon tetrachloride	2.83
Methylene chloride	1.25
Ethylene glycol	-1.36
Propylene glycol	-0.92
Hexylene glycol	0.58
Nitroethane	0.18

Cyclohexanone	0.81
Acetone	-0.24
Xylene	3.15
Toluene	2.73
Benzene	2.13
Petroleum naphthas	4.10-6.15

As can be seen from the K_{ow} values, this painter was exposed to mixtures of lipophiles and hydrophiles. His case history reveals that his exposures ranged from concentrations exceeding TLVs to very low levels of inhalation exposure. He was also dermally exposed, frequently having used naphtha to wash up his hands after work. This man's exposures are typical of many painters and his neurotoxicological symptoms are consistent with those observed in other painters [92-94].

Case 2 [118]

In a study of hospital histology technicians it was found that these workers had greater disturbances of memory, mood, equilibrium, and sleep and had greater frequencies of headaches than other unexposed clerical workers in the same hospitals. The chemicals they were exposed to included:

Formaldehyde	0.35
Xylene	3.15
Toluene	2.73
Ethanol	-0.31
Chloroform	1.97
Methyl methacrylate	1.38

The histology technicians were regularly exposed to mixtures of formaldehyde, toluene, and xylene and less frequently to ethanol, chloroform, and methyl methacrylate. All exposures were at levels below TLVs for the individual chemicals and below levels at which the neurotoxic effects that were observed are expected. All the mixtures to which the histology technicians were exposed contained at least one lipophile and one hydrophile.

Case 3 [119]

An epidemiologic investigation of car and industrial spray painters in Sweden showed that these individuals were always exposed to mixtures of solvents, often to 8-10 different chemicals at the same time and always to mixtures of lipophiles and hydrophiles. The chemicals detected in the workers' breathing zones included:

Toluene	2.73
Xylene	3.15
Styrene	2.95

Ethanol	-0.31
Propanol	0.05
Butanol	0.88
Acetone	-0.24
Methyl- <i>n</i> -butyl ketone	1.38
MIBK	1.19
Ethyl amyl ketone	2.15
Ethyl acetate	0.73
Isoamyl acetate	2.26
Methylene chloride	1.25
1,1,1-Trichloroethane	2.49
TCE	2.42

Though the levels of exposure were found to be considerably lower than Swedish TLVs, the exposed individuals showed increased frequencies of neurological and psychiatric symptoms than unexposed controls.

Case 4 [120]

A group of 15 industrial painters from three different employment sites were evaluated for symptoms related to work and compared with 30 non-painters. Painters at all three sites were exposed to mixtures of lipophilic and hydrophilic solvents. These were:

Site A

Toluene	2.73
Xylene	3.15
MEK	0.29
Acetone	-0.24
Ethyl acetate	0.73
Ethyl benzene	3.15
Isobutyl acetate	1.78
<i>n</i> -Butyl acetate	1.78
Hexane	3.90
Mineral spirits	4.10-6.15
Naphthalene	3.30

Site B

Toluene	2.73
Xylene	3.15
Aliphatic and aromatic hydrocarbons	4.10-61.5
MEK	0.29
TCE	2.42
Methylene chloride	1.25

Site C

Toluene	2.73
Xylene	3.15
Ethyl acetate	0.73
Aliphatic and aromatic hydrocarbons	4.10–6.15

Though the chemicals they were exposed to varied by work site, the symptoms reported and conditions found were identical. All 15 painters reported episodes of headaches, nausea, dizziness, and disorientation. Neuropsychological evaluations showed learning and memory deficits, impaired neuropsychological functioning, and personality problems. Several of the painters were found to have sensorimotor peripheral neuropathies. Though chemicals of exposure at all three work sites included toluene and xylene, some of the symptoms and conditions reported in this study (e.g., peripheral neuropathies) are not consistent with the known neurotoxicology of these solvents. It is concluded that the range of effects experienced by the 15 painters in this study are the result of exposures to mixtures of lipophilic and hydrophilic chemicals.

Case 5 [121]

A study that addressed the cognitive and neurosensory effects of exposure to chemicals used by nail salon technicians revealed effects similar to those observed among solvent-exposed workers in other environments. Nail salon technicians are routinely exposed to low levels of the following lipophilic and hydrophilic chemicals:

Formaldehyde	0.35
Toluene	2.73
<i>n</i> -Butyl acetate	1.78
Ethyl acetate	0.73
Methyl methacrylate	1.38

In this study 33 nail technicians were compared to a similar demographic group that had no known history of exposure to toxic chemicals. Despite concentrations below TLVs for all of the chemicals, the nail technicians performed more poorly on tests of attention and processing speed than the controls did. The nail technicians also had reduced olfaction levels.

Case 6 [122]

The effects of low levels of organic solvent mixtures to which printers were exposed were studied as a function of levels of exposure. The printers were exposed to the following chemicals:

<i>n</i> -Hexane	3.90
Toluene	2.73
Isopropyl alcohol	0.05
Benzene	2.13

Neurological symptoms, including memory loss and reduced olfaction, in the study printers increased with increasing levels of exposure. It is interesting to note that all exposure levels were below TLV. The neurotoxic effects are attributed to the mixture of lipophilic and hydrophilic chemicals. The results of this study concur with a neurotoxic exposure case involving a printer exposed to the same chemicals that I investigated, but have not to date published. In that case, the exposure levels to which the printer was exposed were more than an order of magnitude below the TLVs of all the chemicals.

Case 7 [123]

The irradiation of mail addressed to the Congress of the United States began in November 2001 following the discovery of anthrax spores in some of the mail. While irradiation had successfully been used to disinfect food and medical devices for many years (see Section 10.16), this marked the first such application to mail. Shortly after resumption of mail delivery to Congress, adverse neurological health effects, including headaches and nausea, were experienced by employees handling the mail. Testing was carried out for chemicals that could have potentially come from irradiated mail. These included:

Carbon monoxide	1.78
Formaldehyde	0.35
Ozone	-0.87
PAHs	4.10-6.50
Toluene	2.73

The levels of all tested chemicals were either at low levels or not found. It should be noted that it is probable that other molecular species were also present, as irradiation is known to cleave molecules and produce aldehydes, ketones, and other species which are largely hydrophilic. The study concluded that the health effects noted were not the result of exposures to emissions from irradiated mail, despite the fact that the employees had other clinically evident symptoms, including nosebleed, itching skin, and skin rashes. It is opined here that the low-level mixture of lipophiles and hydrophiles was indeed responsible for the neurotoxic and other effects reported and that the impacts on workers were inappropriately ignored.

Case 8 [124]

A “mystery illness” was reported in a group of casino workers who complained of neurotoxic and respiratory symptoms following the fumigation of the casino with the following mixture:

Propoxur	1.52
Coumaphos	4.13
1,1,1-Trichloroethane	2.49

Methylene chloride	1.25
Xylene	3.15
Acetone	-0.24

Neurologic and neuropsychologic symptoms reported included difficulty concentrating, memory loss, numbness in the face or extremities, shaking, tremors, headache, and sleep disorders. Industrial hygiene evaluation revealed only trace quantities of the chemicals noted, yet pesticide poisoning symptoms were observed.

Cases 9 [125]

Adverse neurological effects were noted in shoemakers exposed to solvents from glues they use. The chemicals contained in these glues included:

<i>n</i> -Hexane	3.90
Cyclohexane	3.44
MEK	0.29
Ethyl acetate	0.73

The symptoms reported included sleepiness, dizziness, headache and weakness, and peripheral neuropathies. These symptoms prevailed despite the low levels of exposure, which were below PEL values. The results reported in this case are similar to those reported for other shoemaker exposures [106, 126, 127].

Case 10 [65]

Low levels of an applied herbicide/pesticide mix were drawn into the air-conditioning makeup air of a commercial building. Workers reported neurological symptoms that included nausea, dizziness, and headaches immediately after the pesticide mix was applied. Chemicals contained in the mix included:

2,4-D	0.65
MCP	3.13
Dicamba	1.13
Naphthalene	3.30
Dinitroaniline	1.29
Solvent naphtha	4.10-6.50

The concentrations of all the chemicals were far below their TLVs.

Case 11 [128]

To assess the combined effect of MPTP ($K_{ow} = 2.71$), which is known to induce PD [31], and the organophosphate pesticide paraquat ($K_{ow} = -2.71$), mice were treated with a low nontoxic dose of MPTP followed by a treatment with paraquat. The study

showed that prior treatment with MPTP potentiated the effects of paraquat on the nigrostriatal dopaminergic system. The authors concluded that these results support the role of toxic mixtures in causing PD.

Case 12 [116]

In a cohort study of men working in a Viscose Rayon plant it was found that 131 workers who were exposed to carbon disulfide ($K_{ow} = 2.00$) and excessive noise were found to have far greater low-frequency hearing losses than 105 workers who were exposed to noise only or 110 workers who were exposed to carbon disulfide, but not noise. Though noise is not a chemical, this case study demonstrates the combined effect of a physical and chemical stress to the body.

Case 13 [134]

A 61-year-old artist who had been painting large canvases in his home studio for 30 years was healthy until the age of 59.5 years of age, at which time he began experiencing the following symptoms:

Weakness and paresthesia in all four extremities
Difficulty concentrating
Impaired memory.

This painter had been exposed to the following chemicals:

Benzene	2.13
Toluene	2.73
Xylene	3.15
Acetone	-0.24
MEK	0.29
TDI	0.21
Paint thinner	3.00-5.00

The authors were unable to find any other similar case report in the literature. TDI is a known respiratory irritant and sensitizer, but is not known to attack the CNS in low concentrations [129, 130]. The low-level exposures to the other solvents could also not account for the observed neurotoxic effects. Clearly, this painter was exposed to a mixture of several lipophiles and hydrophiles that produced this previously unknown effect.

Case 14 [131]

Another example of low-level neurotoxic impact by exposure to isocyanates is the reported exposure of five men to methylene diphenyl diisocyanate, a hydrophile and hydrocarbon solvent, a lipophile. Like TDI, methylene diphenyl diisocyanate is a respiratory irritant and sensitizer, but not generally associated with sympathetic

nervous system effects. The five individuals reported in this case study suffered respiratory distress as well as the following neurological symptoms:

- Headache
- Depression
- Emotional distress
- Irritability
- Memory loss
- Decreased ability to carry out calculations
- Word-finding problems
- Reduced concentration ability.

It is believed that the combination of the hydrophilic methylene diphenyl diisocyanate and the lipophilic hydrocarbon solvent are responsible for the unanticipated CNS effects.

18.8 Summary

Multiple neurotoxic effects can be induced by exposures to mixtures of lipophilic and hydrophilic chemicals at levels below those known to be neurotoxic for the individual chemicals. It is hypothesized that lipophilic chemicals facilitate the absorption of hydrophilic species, resulting in the uptake of greater quantities of hydrophiles than would occur in the absence of the lipophiles. Neuropathies, behavioral changes, and NDDs have been shown to be caused by these mixtures, often via unknown mechanisms. Both acute and chronic low-level effects following exposures to such mixtures have been reported. Since exposures to chemicals almost always are to mixtures, the need to lower the TLVs for neurotoxic chemicals is indicated.

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19 Developmental Neurotoxicology

Chapter Outline

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19.1 Introduction

Children are not miniature adults. Neurotoxic effects induced by xenobiotic chemicals in adults may not be indicative of the effects on the developing nervous system, which spans from conception through adolescence. Conversely, there are chemicals that are neurotoxic to the developing fetus and the growing child that are benign to adults. The CNS is the most vulnerable of all body systems to developmental injury, and the developmental neurotoxic effects to it are influenced by the timing of the exposures as well as the dose. Exposures during the development of a particular part of the nervous system can have extreme effects, while the same exposures at other times can be benign. For example, maternal exposure to the DDT metabolite, DDE, affects psychomotor development only when exposure is in the first trimester of pregnancy [1]. Neurotoxic effects can be delayed in onset and manifest themselves at any time throughout one's life span [1–4].

Exposures to developmental neurotoxins are believed to be responsible for staggering numbers of affected children. In the United States, 5–10% of public school children have learning disabilities, up to 17% of children suffer from ADHD, approximately 1% of all children are mentally retarded, and as many as 1 in 150 children born have autism [5, 6]. Though some of these effects are genetically influenced, the available evidence suggests that environmental exposures and not genetics are the primary causes for these disorders [5].

A large number of individual chemicals are recognized as developmental neurotoxins. These include heavy metals, alcohol and other solvents, recreational drugs (e.g., nicotine and cocaine), pesticides, and some pharmaceuticals. Table 19.1 contains a partial list of these and some of the effects ascribed to them [1, 5, 7–21].

19.2 Mixture Neurotoxicity

Though most environmental exposures are to mixtures, most developmental neurotoxicity studies have addressed only single chemicals. Only a very few have addressed the

Table 19.1 Partial List of Known Developmental Neurotoxic Chemicals**Metals**

Cadmium	Learning disabilities Decreased IQ
Lead	Learning disabilities Hyperactivity and aggression
Manganese	Brain damage Memory impairment
Mercury	Motor dysfunction Learning and memory disabilities

Solvents

Ethanol	Attention deficits and behavioral disorders Memory impairment
Styrene	Decreased activity Behavioral disorders
Toluene	Speech and motor dysfunctions Learning disabilities
TCE	Hyperactivity Behavioral disorders
Xylene	Learning and memory impairments Motor dysfunction

Pesticides

Bioallethrin	Hyperactivity
Chlorpyrifos	Decreased coordination
DDT	Hyperactivity Memory and coordination impairment
DDE	Motor dysfunction
Deltamethrin	Hyperactivity
Diazinon	Decreased coordination Memory impairment

Miscellaneous

Dioxins	Learning disabilities
Fluoride	Hyperactivity Decreased IQ
Nicotine	Hyperactivity Learning and cognitive disabilities
PCBs	Memory and learning impairments Psychomotor dysfunction
Carbon monoxide	Brain damage Behavioral disabilities

effects of mixtures and even fewer have reported quantitative data on concentrations and dose levels. The following is a review of the literature on the subject.

It has been known for more than 25 years that maternal exposures to some solvent mixtures during pregnancy result in children being born with CNS defects [22].

Table 19.2 CNS Birth Defects Following Maternal Exposure to Solvent Mixtures During Pregnancy

Case	Industry	Solvents	K_{ow}	CNS Defect
1	Plastics manufacturing	Styrene	2.95	Congenital
		Acetone	-0.24	Hydrocephaly
2	Leather	Denatured ethanol	-0.31	Anencephaly
		Dyes	L,H	
3	Textile	Ethylene oxide	-0.30	Hydrocephaly
		Dyes	L,H	
		Alkylphenols	1.95	
4	Laboratory	Benzene	2.13	Anencephaly
		Methylene chloride	1.25	
		Diethyl ether	0.89	
		Methanol	-0.77	
5	Museum	White spirit ^a	L	Congenital
				Hydrocephaly
6	Plastics manufacturing	Styrene	2.95	Anencephaly
		Acetone	-0.24	
7	Printing and publishing	White spirit ^a	L	Meningomyelocele with hydrocephaly
8	Rubber products	Toluene	2.73	Hydrocephaly
		White spirit ^a	L	
		MEK	0.29	
		Xylene	3.15	
9	Metal products	Petroleum	L	Meningomyelocele
		Denatured ethanol	-0.31	
10	Leather	Denatured ethanol	-0.31	Hydrocephaly
		Dyes	L,H	
11	Building	Toluene	2.73	Meningomyelocele
		White spirit	L	
12	Home handicrafts	Styrene mixed	2.95	Anencephaly
and		Mixed aliphatic/	L	
13		aromatic hydrocarbons		

Source: Ref. [22].

L, lipophilic mixture; L,H, mixture of lipophilic and hydrophilic species.

^aWhite spirit is a mixture composed primarily of C₉-C₁₂ hydrocarbons.

Table 19.2 summarizes the data reported by Holmberg in 1979, who first identified this phenomenon. K_{ow} values were not included in the Holmberg paper, but are added here to show lipophilicity and hydrophilicity. Holmberg identified 13 mothers who had been exposed to solvent mixtures on the job during pregnancies and the resultant CNS defects in their children. It should be noted that his report included one mother who was exposed only to toluene, a chemical that has since been established as teratogenic [4, 5].

It is noteworthy that most of the exposures in the Holmberg study were to mixtures of lipophiles and hydrophiles.

Other studies that have addressed the developmental neurotoxicities of chemical mixtures include the following:

1. Exposure to PCBs during gestation and lactation is known to induce neurobehavioral effects. A mixture of 14 PCBs and 11 organochlorine pesticides (aimed at simulating the blood levels reported in Canadian populations living in the Great Lakes/St. Lawrence basin), however, was shown to be more toxic than Arochlor 1254 (a commercial PCB mixture) alone, and to induce a different profile of effects on early neurodevelopment in laboratory animals [23]. All the organochlorine pesticides are lipophilic as can be seen from the following K_{ow} data:

Aldrin	6.50
DDT	6.91
DDE	6.51
Dieldrin	5.20
Heptachlor epoxide	4.98
HCB	5.73
Mirex	7.18
<i>cis</i> -Nonachlor	6.20
<i>trans</i> -Nonachlor	6.20
Hexachlorocyclohexane	3.72
Oxychlordan	5.48

All PCB congeners are also lipophilic, as was the corn oil used to dissolve the mixture. The mixture, however, was not completely soluble in the corn oil and 5% diethyl ether was used as a solvent to ensure complete solubility and homogeneity. Diethyl ether is a hydrophile, with a K_{ow} of 0.89. The role played by the diethyl ether in the mixture effects is not known.

2. Children living in agricultural communities are regularly exposed to pesticide mixtures through airborne and take-home sources. Neurobehavioral performances of Latino preschool children of agricultural workers in North Carolina and Oregon were found to be poorer than those living in non-agricultural communities in the same areas [24]. Agricultural pesticides are most often applied as mixtures. Combined with their solvents, surfactants, and other additives, they are almost always mixtures of lipophiles and hydrophiles (see Chapter 14).
3. Elevated odds ratios for neural tube defects were higher in children whose fathers worked at jobs that exposed them to chemical mixtures than in children whose parents did not work in such jobs. In a California study it was found that the children of farm workers, janitors, cooks, and groundsman/gardeners, all of which jobs exposed these workers to mixtures of lipophilic and hydrophilic chemicals, had higher incidences of neural tube defects than in the children of managers and professionals. Other factors, including race, ethnicity, maternal health, maternal exposures to toxic chemicals, and education levels, were ruled out as contributing factors [25].
4. Perinatal exposure of mice to dieldrin alters the dopaminergic neurochemistry in their offspring. Exposure to a mixture of dieldrin and MPTP during development exacerbates the neurotoxicity of MPTP, a known chemical cause of PD. This study serves as a model for the induction of PD by chemical mixtures [26].
5. A second study related to PD involved the effects of a mixture of the herbicide, paraquat, and the fungicide, maneb (a combination commonly applied to crops). Both paraquat alone and maneb alone adversely affect dopamine systems, but the effects of the mixture are greater than that of either pesticide alone [27].

It is often difficult to ascribe neurodevelopmental deficits to chemical exposure only. Genetic makeup predisposes some individuals to chemical insult effects. Autism and ADHD are the two prominent examples of developmental conditions that fit such a hypothesis. Both affect large numbers of children, and their prevalences can be linked to environmental chemical exposures. These are discussed in the following chapters.

19.3 Summary

The developing fetus and the growing child are at greater risk than adults are from exposures to neurotoxic chemicals. Relatively little is known about developmental neurotoxic effects of single chemicals and even less about the effects of chemical mixtures.

Very few studies have been carried out on the developmental neurotoxicity of chemical mixtures. Those that have been reported, however, have demonstrated enhanced or unanticipated neurotoxic effects following mixture exposures.

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20 Autism: Effect of Maternal Exposure to Neurotoxic Chemicals

Chapter Outline

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20.1 Autism

Autism spectrum disorder (ASD) is a neurodevelopmental syndrome characterized by communication and social interaction impairments, abnormal movements, repetitive behaviors, and sensory dysfunction [1–3]. It usually manifests itself from 18 months to 3 years, and it is more prevalent in boys than girls and involves noticeable brain differences in those who have it [3]. All autism disorders—autism, Asperger syndrome, other autism-like conditions/atypical autism—may approach 1% of school populations in some areas [4, 5]. In 2007 it was estimated that there is a range in prevalence of 1 in 500 to 1 in 166 children born in the United States [6]. In 2010 it was estimated that 1 in 110 children and 1 in 70 boys born will be afflicted with ASD [7]. Though some of the increases being reported in some areas may be attributed to better diagnoses and record keeping, it is estimated that autism prevalence in the United States is increasing by 17% annually [6].

Autism is seemingly found in every part of the world though its prevalence varies. The highest autism rates are found in the industrialized, developed countries of the world. Though found in the indigenous populations of Africa, the rates there are low [8]. Autism is also virtually unknown in the Amish and Mennonite communities of Pennsylvania and Ohio (D.H. Morton, Clinic for Special Children, Strasburg, PA, July 2004, personal communication) [9]. Several researchers have noted a tendency for parents of autistic children to be highly educated and of higher socioeconomic groups [8, 10].

Autism prevalence data from around the world and, indeed, even within individual countries and states, are sporadic, but they indicate rising rates almost everywhere. For example, autism rates in Iceland increased from 3.8 per 10,000 in the period of 1973–1983 to 8.6 per 10,000 in the period of 1984–1993 [11]. Thirty-one cases of

autism per 10,000 births were reported in Sweden in the 1990s [12]; an autism rate of 11.3 per 10,000 births was reported for people native to southern Japan [13]; and rates of 30 per 10,000 in U.S. metropolitan areas were reported in 2003 [14].

It is generally agreed that autism has been increasing worldwide at least since 1979 at a rate of 3.8% per year [15, 16]. As of 2002, the conservative estimate of worldwide prevalence was 10 per 10,000 births [17]. It has since dramatically increased [18].

The available data, however, point in the direction that autism prevalence is lower in rural than in urban areas within the same locale. Autism is prevalent at the rate of 3.06 per 10,000 in the urban areas of Kukishama-Ken in northern Japan and at a rate of 1.18 per 10,000 in rural areas of this region [17]. In this study, it was noted that autism rates were lower when parents worked in agriculture, forestry, fishing, or mining, all presumably rural areas. Among the indigenous peoples of Africa, autism rates are lower than in other parts of the world [8].

Autism is generally believed to have a strong genetic component. Its associated neurological effects are believed to occur in early embryonic development, at 20–24 days of gestation [19]. The initiating injury for autism occurs around the time of neural tube closing [20]. Parents with autism or Asperger syndrome pass these along to offspring [21], and men with Asperger syndrome produce children that are more likely to develop autism [22]. Autism is related to above average head size, something that seems to reflect a large brain. This could be due to a deficit in neural cell pruning brought on by exposure to environmental chemicals [23].

Autism, however, is not believed to be attributable solely to inherited traits [24, 25]. It has been suggested that though a genetic factor is essential, a second deleterious environmental exposure produces a genetic–environmental interaction that ultimately produces autism [3, 16, 22, 26, 27]. Several researchers have suggested that autism may be subject to environmental influences that can include viruses, hormones, intrauterine stresses, and toxicants [27]. Included among these are maternal use of cocaine [28, 29], exposure to rubella virus, valproic acid, or thalidomide during pregnancy [19].

Maternal neurotoxic chemical exposures are also suspected of being associated with increased rates of autism [23]. Here, the case is made for maternal environmental exposure to neurotoxic chemicals as a contributing factor. It has been well established that neurotoxins cause brain damage in the developing fetus and that in the developing fetus the CNS is the most vulnerable of all body systems to injury. Ethanol, cocaine, nicotine, thalidomide, isotriternair, mercury, manganese, lead, dioxins, PCBs, toluene, TCE, xylene, arsenic, carbon tetrachloride, benzene, dichloroethylenes, PCE, trihalomethanes, HAAs, chlorophenols, chloral hydrate, HANs, and perchlorates are but a few of the chemicals known to cause fetal brain damage [23, 30–34]. Prenatal exposure to PCBs has been shown to lower IQ in the offspring [33]. Maternal use of the antiepileptic drug, phenytoin, results in a 10-point decrease in IQ in offspring [35].

Neurotoxic agents can act differently in children than in adults because of their effects on developments, which have no parallels in adults [30]. The developing fetus is more sensitive to neurotoxic agents than adults or even young children [23]. Low levels that are not harmful to adults negatively affect the developing brain [31].

Different chemicals can cause different injuries at different parts of the fetus's development; that is, different parts are sensitive at different stages of development. A given neurotoxic agent can cause multiple effects, and neurodevelopmental consequences of exposure may vary, since different areas of the brain develop at different times and since dose and timing lead to different outcomes [30, 34, 36]. The nervous, immune, endocrine, and reproductive systems are extensively interconnected and interference with any one of these can have profound effects on any or all of these systems [37].

20.2 Chemical Mixtures

Mixtures of chemicals have been shown to produce neurotoxic effects that are not predicted from the known toxicology of the mixtures' individual chemicals. Low concentrations of chemical mixtures produce unusual and unexpected CNS effects [38–41]. These effects are confounded by concurrent exposure to other toxic chemicals [42].

It is estimated that 28% of all chemicals used in commerce could be neurotoxic [43]. Common household products including air fresheners, fragrance products, marking pens, and mattress covers contain known neurotoxins [44–47]. The neurotoxic effects of marking pens are attributed to chemical mixtures [47]. Aspartame, saccharin, artificial food colors, benzyl alcohol, and other excipients used in pharmaceutical preparations and foods are neurotoxins [48, 49].

Superfund sites are sites that emit numerous neurotoxins into the air and water environments. Love Canal studies have shown nervous system effects that can be attributed to living near a toxic waste site [37]. Elevated neural tube defects in offspring were identified with mothers residing proximate to hazardous waste sites [50, 51]. It has also been shown that people residing close to industrial facilities that emit solvents or metals have offspring with increased CNS defects [52].

The following studies relate autism to environmental factors:

1. In a study in southern Japan, the prevalence rate for natives to the area was 11.3 per 10,000 births. The rate for migrants to the same area was 17.6 per 10,000 births. The native rates fluctuated from year to year in a 4-year cycle, whereas the migrant rates did not. In this study, children born in the second quarter of the year had a higher rate of autism than those born in other times of the year. It was also found that the prevalence of autism was closely related to the number of hospital admissions for pneumonia and bronchitis in the children affected [13]. The rate fluctuations reported in this study cannot be attributed to genetic factors.
2. The literature reports that 36–91% of the time, both monozygotic (MZ) twins are autistic [3, 53–55]. If genetics were the only factor, one would expect dual autism in all MZ twins.
3. The prevalence of autism in an area of northern Japan was studied. The overall prevalence was 2.33 per 10,000 births. The case in the cities, however, was 3.06 per 10,000, and characteristically in rural areas was only 1.18 per 10,000. Autism prevalence was found to be relatively low when parents had rural jobs (forestry, fishing, or mining) and relatively high when fathers had jobs for which higher education is generally required (perhaps relating to urban residence). This study showed that autism rates varied from year to year [17]. Both these factors, the greater autism prevalence in urban than in rural children and the year to year fluctuations in rates, cannot be attributed to genetic factors.

4. Lotter [8] reported that though autism is found in the indigenous people of Africa, the prevalence seems to be less than in more-developed parts of the world. He also reported that the prevalence of autism in Africa was less in the rural areas than in the urban areas of the continent. Here again, the greater preponderance of autism in urban than in rural areas cannot be attributed to genetics.
5. Autism is virtually unknown in the Amish and Mennonite communities of Lancaster County, Pennsylvania [9]. In these communities, no incidences of autism have been reported in more than 16,000 births from 1988 to 2004. The Amish and Mennonite autism data are the result of 16 years of record keeping among the Amish in Lancaster County, Pennsylvania by Dr. D. Holmes Morton of the Clinic for Special Children in Strasburg, Pennsylvania. This clinic sees every child in the Amish and Mennonite communities in Lancaster County, Pennsylvania with neurological disorders. The Amish and Mennonites live in rural communities. They do not use chemicals or electricity in their daily lives, use only organic farming techniques, and abstain from tobacco and recreational drugs. The absence of autism in these communities strongly suggests a relationship between autism and environmental factors. The Amish and Mennonite communities are insular. Accordingly, it is possible that the lack of autism in these groups could be strictly genetic. This is considered unlikely, however, since they are of German extraction genetically and prevalence of autism in Germans is similar to that in other Western populations.
6. It has been reported that maternal use of cocaine has resulted in an 11.4% rate of autism for offspring [28]. This extremely high rate of autism far exceeds any rate reported in all other studies reported, and strongly suggests an environmental factor.
7. Stromland et al. [19] have reported that children exposed to thalidomide between 20 and 24 days of gestation show a very high rate of autism. Of 86 children so exposed, four subsequently developed autism, a rate that cannot be accounted for by genetics alone.
8. The state of California systematically monitors, collects, and reports autism data statewide on a consistent basis, with the number of cases diagnosed in each county reported on a quarterly basis [56]. The data show lowest autism rates for rural counties, higher values for urban and highly populated suburban counties, and much higher values for Los Angeles County. In 1999 and again in 2003, California issued reports on the prevalence of autism in the state [57, 58]. These reports show autism increasing in the state at the rate of about 3% per year, with the increases greatest in Los Angeles County, lower in the other urban and highly populated suburban counties, and least in the rural counties of the state. Table 20.1 summarizes the California data for the period 2003–2004. This table includes the numbers of autism cases by county and statewide for each of the 2 years, the percent increase of autism by county and statewide, population data for the 2 years, and autism cases per million population in 2004.

The increases in autism prevalence in California have, for the past 20 years, been correspondingly greater in the more highly urbanized areas than in rural areas. The alarmingly high autism prevalence in Los Angeles County is consistent with this observation. These large increases cannot be attributed to improvements in detection, as has been proposed [51], nor can this be attributed to ethnicity, racial identity, or immigration status as has been previously suggested in a much smaller studies [12, 21]. Higher maternal age as has previously been suggested [12], however, can also be ruled out due to the very large annual increase in California autism without a concurrent increase in maternal age. Genetic, mutational changes, or other factors similarly cannot account for the increase in California. During the 1-year period, April 2003–April 2004, the population of California grew by only 1.5% [59], yet autism prevalence increased by 13%. As can be seen from the data in Table 20.1, for the time period, 2003–2004, the population increases in every county were far below the increases in autism cases. Various reasons have been proposed to account for

Table 20.1 Autism Prevalence Rates for California, 2003–2004, Population Data and Autism Cases per 1,000,000 Population in 2004

County	Autism Cases 2003	Autism Cases 2004	Autism % Increase 2003–2004	Population 2004—36,000,000	Population % Increase 2003–2004	Autism Cases per 1,000,000—2004
Alameda	719	816	14	1,498,700	0.7	483
Alpine	0	1	^a	1280	0.0	^a
Amador	3	7	^a	36,850	0.5	110
Butte	111	128	15	212,700	0.9	533
Calaveras	17	24	^a	43,350	1.4	163
Colusa	3	3	^a	20,100	1.8	152
Contra Costa	517	582	13	1,003,900	1.1	586
Del Norte	11	11	^a	28,250	0.9	393
El Dorado	35	37	7	168,100	1.3	223
Fresno	212	281	33	862,600	2.0	332
Glenn	12	12	^a	27,750	1.3	438
Humboldt	80	88	10	130,000	0.9	683
Inyo	4	5	^a	18,500	0.3	271
Kern	365	423	16	724,900	2.3	597
Kings	33	44	33	141,400	2.0	240
Lake	17	18	6	63,200	1.4	289
Lassen	6	11	^a	34,850	2.0	322
Los Angeles	9375	10,663	14	10,103,000	1.4	940
Madera	21	28	33	135,300	2.9	213
Marin	84	87	4	250,200	0.2	338
Mariposa	8	11	^a	17,650	0.6	627
Mendocino	37	41	11	89,200	0.9	464
Merced	81	95	17	232,100	2.2	419
Modoc	1	1	^a	9650	1.0	105
Mono	6	5	^a	13,500	0.7	373
Monterey	90	103	14	421,400	1.4	249
Napa	54	65	17	131,600	1.2	494
Nevada	16	20	25	96,100	1.1	208
Orange	2067	2216	7	3,017,300	1.4	734

(Continued)

Table 20.1 (Continued)

County	Autism Cases 2003	Autism Cases 2004	Autism % Increase 2003–2004	Population 2004—36,000,000	Population % Increase 2003–2004	Autism Cases per 1,000,000—2004
Placer	98	122	24	292,100	3.0	418
Plumas	4	5	^a	21,100	0.5	237
Riverside	689	825	20	1,776,700	3.4	464
Sacramento	584	714	22	1,335,400	1.8	535
San Benito	18	24	33	57,100	1.4	420
San Bernardino	795	928	17	1,866,500	2.4	492
San Diego	1377	1529	12	3,017,200	1.4	462
San Francisco	191	215	13	792,700	0.4	242
San Joaquin	256	352	38	630,600	2.3	558
San Luis Obispo	94	116	23	258,200	1.1	449
San Mateo	223	267	20	712,400	0.5	375
Santa Barbara	232	258	11	414,800	1.1	622
Santa Clara	750	906	21	1,731,400	0.7	523
Santa Cruz	102	114	12	260,200	0.5	438
Shasta	82	88	7	175,700	1.4	501
Sierra	1	1	^a	3520	–1.1	284
Siskiyou	10	12	20	44,850	0.6	268
Solano	193	222	15	416,500	1.0	533
Sonoma	314	355	13	472,700	0.7	722
Stanislaus	243	305	26	491,900	1.8	620
Sutter	29	30	3	85,500	2.0	351
Tehama	17	18	6	58,700	1.4	307
Trinity	2	3	^a	13,450	1.1	223
Tulare	121	148	22	396,800	2.1	373
Tuolumne	19	22	16	56,900	0.5	387
Ventura	623	713	14	802,400	1.4	889
Yolo	75	82	9	184,500	1.9	444
Yuba	16	19	19	64,800	1.6	293
Statewide	21,209	24,297	13	36,144,000	1.5	672

^aNumbers too small to be statistically meaningful.

the greatly increased rates in California. These include the suggestion that factors such as hormone levels, diet, and lack of early prenatal care in some groups could be responsible [51]. None of these, however, are supported by the data.

The data in Table 20.1 show the rates of autism are much lower in the rural counties than in the urban ones and that the autism rates in Los Angeles and the surrounding counties (Orange and Ventura) are much higher than those in other urban areas. It should be noted that the autism rates in San Francisco and the surrounding counties (Marin and Santa Cruz) are lower than those in other urban areas, yet even there the rates continue to rise.

It is suggested here that the dramatic increase in autism in California is due to environmental factors. The highly populated areas of California have poor air and water quality, contain numerous neurotoxic chemicals [60–63], and are in close proximity to numerous Superfund sites [60]. This is particularly the case in the Los Angeles area.

9. High rates of autism were suspected in five counties of metropolitan, Atlanta, area [14] and in Brick Township, New Jersey [64]. The data collected show that the values for the Atlanta area and for the Brick Township are similar to those for other large urban areas, including California, other than the Los Angeles area [33]. These high values are attributed to Atlanta's air pollution [65] and Brick Township's proximity to several Superfund sites [66].

As noted earlier, there is a tendency for parents of autistic children to be highly educated and of higher socioeconomic groups [8, 10]. This is perhaps so because more highly educated and upper socioeconomic groups tend to live in more environmentally contaminated urban locations than others.

20.3 Summary

Cocaine and thalidomide have been identified as causative agents for autism [19, 28]. While other specific environmental chemicals have not yet been definitively identified, one should expect that additional individual chemicals and mixtures of chemicals will be discovered as time goes on. It has been shown that mixtures of lipophilic and hydrophilic chemicals can cause neurotoxic effects at very low concentrations and in ways in which the individual components of the mixtures do not by themselves so act [38–40]. It has also been shown that exposures to specific mixtures of otherwise benign single chemicals have many toxic consequences, including neurotoxic effects [38]. Of the almost infinite number of toxic chemical mixtures possible in the environment, only a very few have been demonstrated to be toxic. If one properly includes food, tobacco, pharmaceuticals, excipients, and recreational drugs in the equation and considers previously published findings [38–40, 67], it is reasonable to assume that at least some of these mixtures do have neurotoxic consequences. It is suggested here that maternal exposures to as yet unspecified chemical mixtures increase the prevalence of autism.

Autism certainly has a genetic factor associated with it. Studies, however, showing seasonal and annual variations in its prevalence, increased prevalence in urban versus rural areas, increased prevalence in areas with increased environmental pollution, and increased prevalence in offspring of mothers who have taken certain drugs, lead to the conclusion that there is a connection between the maternal environmental exposure to neurotoxic chemicals and the prevalence of autism.

A discussion of the environmental causes of autism would not be complete without addressing the question of whether or not thimerosal, a mercury-containing preservative, which was incorporated into childrens' vaccines for measles, mumps, and rubella (as well as in other vaccines) for many years, is a causative agent. Mercury exposure has been identified with an increased prevalence of autism. In a Texas study, it was found that environmental releases of mercury are related to an increase of more than 60% in the autism rate in the area of release [68]. The effect of mercury from childhood vaccines that contain thimerosal as a possible trigger for autism has been researched and debated extensively. Some believe that thimerosal is not an autism trigger [69] because the autism rates have continued to climb after its use in childrens' vaccines was discontinued. Others argue that it is plausible that thimerosal is a causative agent for autism [70, 71]. Recently, however, autism has been associated with a urinary porphyrin pattern indicative of mercury toxicity in a large cohort study of French children. In that study, coproporphyrin levels were significantly elevated in children with autism compared to control groups [72]. These results have been duplicated in an American study [73]. The reasons for the elevated mercury levels in the autistic children in these studies are unknown. All children had no known significant mercury exposure other than from thimerosal-containing vaccines that they were given. Why the autistic children and not the non-autistic children (who were also given thimerosal-containing vaccines) retained the mercury in their systems is also unknown. A recent study has found that blood levels of mercury alone are similar in children with ASD and free of ASD, even when dietetic consumption of mercury (through the eating of fish) was taken into consideration [74]. To date, no one has studied the effects of mixtures of thimerosal with other chemicals.

As of this time (2011) it is felt that mercury alone is not the cause of the increased incidence of autism, but that environmental factors are. The average prevalence of ASD increased 57% in children aged 8 years from 2002 to 2006. This cannot be accounted for by genetics or better reporting [75]. Recent research has tied autism prevalence to exposures to inflammatory agents (chemical and biological) that have also been tied to asthma rate increases [76]. It has been suggested that acetaminophen, which is suspected as causing an increase in asthma, may also be responsible for increases in autism, particularly since the exponential rise in autism corresponds with the increase of acetaminophen in children [77–81]. This, too, remains an open question at this time, with research ongoing.

A study of almost 5000 children in Sweden has shown that indoor air pollutants are known to cause asthma in that group, and may also be causative for ASD. The factors identified included secondhand cigarette smoke, PVC flooring in the home, and low ventilation rates [78]. Though the studies just cited do not "prove" the associations described, they are strongly suggestive and warrant the more intensive investigation that is currently ongoing.

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21 Attention Deficit Hyperactivity Disorder

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21.1 Introduction

ADHD is a neurodevelopmental and behavioral disorder that is characterized by poor concentration and hyperactivity. Children with ADHD are impulsive and easily distracted to degrees that are greater than expected for their age. These children often daydream and are slow to complete tasks.

21.2 Prevalence of ADHD

ADHD is a worldwide disorder. Estimates for ADHD prevalence worldwide vary from 1.5% to almost 20% [1–6]. The prevalence of ADHD in the United States is estimated by the U.S. Centers for Disease Control and Prevention (CDC) to be 7.74% for all school-age children (about 4.4 million children) [7]. A study published in 2007 determined that almost 9% of all U.S. children suffer from ADHD [8]. It is not yet known why the range of prevalences reported vary as much as they do. They may be due to actual differences or variations in diagnosis and data collection.

In the United States, some 44% of the children diagnosed with ADHD are treated with methylphenidate (Ritalin) or similar drugs [7]. Table 21.1 shows the CDC data for percentages of children diagnosed and treated with drugs in each state [7]. As can be seen from the data, the number of children diagnosed and treated with drugs varies widely. As with the worldwide data, the reasons for the variations in prevalence are not known. The differences in the numbers treated may represent variations in environmental exposures and local culture in dealing with ADHD.

Table 21.1 CDC Data for ADHD Cases Diagnosed and Treated in Each State in the United States

State	% Diagnosed with ADHD	% Treated with Drug for ADHD
Alabama	11.09	6.48
Alaska	7.07	3.95
Arizona	5.89	3.02
Arkansas	9.88	6.51
California	5.34	2.13
Colorado	4.95	2.75
Connecticut	7.38	3.26
Delaware	9.74	5.97
Florida	9.21	4.82
Georgia	9.37	5.57
Hawaii	6.14	2.71
Idaho	6.38	3.66
Illinois	6.32	3.32
Indiana	7.93	4.96
Iowa	8.35	5.52
Kansas	8.14	5.34
Kentucky	10.12	4.77
Louisiana	10.31	6.34
Maine	7.92	4.48
Maryland	9.11	5.84
Massachusetts	8.51	5.43
Michigan	9.21	5.32
Minnesota	7.93	4.67
Mississippi	9.59	5.38
Missouri	7.67	4.53
Montana	7.09	4.38
Nebraska	6.39	4.29
Nevada	7.22	3.33
New Hampshire	9.14	5.67
New Jersey	7.22	3.10
New Mexico	6.10	3.48
New York	6.27	3.39
North Carolina	9.54	6.14
North Dakota	9.39	4.38
Ohio	8.88	4.97
Oklahoma	8.11	4.08
Oregon	7.15	3.83
Pennsylvania	8.17	5.34
Rhode Island	9.81	5.86
South Carolina	9.98	6.24
South Dakota	6.49	4.24
Tennessee	9.87	4.79
Texas	7.69	4.87

(Continued)

Table 21.1 (Continued)

State	% Diagnosed with ADHD	% Treated with Drug for ADHD
Utah	5.49	3.06
Vermont	6.90	3.79
Virginia	9.28	5.46
Washington	7.18	4.03
Washington, DC	6.74	3.48
West Virginia	10.08	5.81
Wisconsin	8.06	4.66
Wyoming	7.13	3.98
Total	7.74	4.33

ADHD is not limited just to children. It has also been estimated that 4.4% of adults aged 18–44 in the United States experience symptoms and some disability of ADHD [9].

21.3 Environmental Factors in ADHD

ADHD is a heritable disorder. Recently published research has shown that children with ADHD have a significantly higher rate of missing or duplicated DNA segments compared to other children. A genetic link between these segments and other brain disorders has also been shown [10]. Available evidence, however, strongly points to environmental as well as genetic factors as causative agents for ADHD. The studies with twins are compelling. MZ twins share all of their genes and dizygotic (DZ) twins share half of their genes. If ADHD were due strictly to genetic factors, one would expect to find 100% concordance for ADHD in MZ twins and 50% concordance in DZ twins. This is not, however, the case. The concordance among twins has been reported in several studies and averages 66% for MZ twins and 28% for DZ twins. These concordance numbers are high enough to establish genetics as a factor, while at the same time low enough to establish environmental factors as causative for ADHD [11–13].

Beyond the genetic factors, the causes of ADHD are unknown, and very few studies have examined the relationship between ADHD and exposures to environmental chemicals. It is known, however, that maternal prenatal exposures to lead, alcohol, tobacco smoke, and marijuana are known to result in the birth of children with high incidences of ADHD [14–17]. It has also been established that exposure to excessive quantities of phenylalanine either prenatally in utero, as a result of the mother having phenylketonuria (PKU) and fetus not having PKU, or postnatally where the child has PKU, results in the development of ADHD hyperactive and behavioral symptoms [18, 19]. The mechanisms for these effects remain unknown, but these reactions to specific agents further demonstrate that environmental exposures may be triggers for ADHD. It is also known that many different chemicals trigger developmental

neurotoxic effects (see Chapters 19 and 20) and it is accordingly reasonable to conclude that there may be many single chemicals and chemical mixtures that are environmental triggers for ADHD. The following section discusses the evidence of synthetic dietary components as such triggers.

21.4 Chemical Mixtures as Triggers for ADHD

It has already been noted that maternal tobacco and marijuana smoking are causative agents for ADHD symptomology [16, 17]. Tobacco and marijuana smoke are very complex chemical mixtures containing more than 4000 different chemicals. The ADHD causative agents in these are unknown. Xenobiotic chemicals present in foods, however, are fewer in number, more easily identified, and have been tested as agents that induce the symptoms of ADHD.

In 1975, Feingold [20] published a remarkable paper in which he asserted that exclusion of artificial colors, artificial flavors, and preservatives from the diets of hyperactive children could significantly benefit as many as half of the affected children. Feingold's assertion provoked extensive scientific and medical attention as well as wide media coverage and dispute. It has, however, withstood many challenges and the test of time. Feingold's published results were based on large numbers of children he had successfully treated clinically by removing artificial colors, flavors, and preservatives from their diets. Though there are still some who deny that synthetic food colorants and preservatives are triggers for hyperactivity, it is generally accepted in the scientific and medical communities that withholding these chemicals from the diets of children with ADHD can substantially reduce the symptoms in many of them. Two excellent reviews that summarize and critique the research that has been carried out have been published. This includes work reported by those whose work has substantiated Feingold's hypothesis [21–24] as well as by those work has challenged Feingold's hypothesis [25, 28]. The reader is referred to the literature for the reviews noted, both of which have strongly established the validity of Feingold's hypothesis [29, 30].

The position taken here is that published by Weiss [29] and Schnoll, Burshteyn, and Cea-Aravena [30]; that is, that the three points of Feingold's hypothesis are supported by experiments that meet the criteria for scientific validity. These are:

1. Many children who are diagnosed as hyperactive improve when given a diet devoid of artificial food colors, artificial flavors, and synthetic preservatives.
2. Some children become hyperactive, at least in the short term, following ingestion of artificial food dyes.
3. Younger children are seemingly more sensitive to artificial food colors, artificial flavorants, and synthetic preservatives than older ones.

The most recent research that has been published is not only supportive of the view that synthetic colors, flavors, and preservatives do indeed impact hyperactive behavior in some children but also demonstrates synergistic effects between artificial colors and other synthetic additives.

In one study [31], significant synergy was observed when the following commonly used mixtures of artificial food colors and flavorants were introduced in vitro:

- a. Brilliant blue and L-glutamic acid (MSG)
- b. QY and aspartame.

Very little has been published about the neurotoxicity of artificial food colors, but L-glutamic acid and aspartic acid are well-established neurotoxins. (Aspartame is rapidly hydrolyzed to release aspartic acid and two other neurotoxins, phenylalanine and methanol.) The two mixtures noted earlier synergistically inhibited the neurite outgrowth in mouse NB2a neuroblastoma cells to far greater extents than L-glutamic acid and aspartame did alone without the addition of the artificial food colors.

In the second study, a double-blind, placebo-controlled one on 4-year-old children, it was found that the combination of 5 mg each of sunset yellow, tartrazine, carmoisine, and Ponceau 4R (artificial colors commonly used to color soft drinks) plus 45 mg of sodium benzoate (a commonly used soft-drink preservative) induced hyperactivity in a statistically relevant number of children [32].

The two studies just cited are relevant because food colors, flavors, and preservatives are typically used in combination in processed foods. Such foods are generally consumed with other foods containing additional synthetic chemicals. Table 21.2 contains a list of artificial food colors, flavors, and preservatives widely used in processed food. None have any nutritional value and all have been shown to be toxic. The K_{ow} values in the table show that all the colors and flavors are hydrophilic and the

Table 21.2 Artificial Food Colors, Flavors, and Preservatives and Their K_{ow} Values

	K_{ow}
Colors	
Brilliant blue	-1.50
QY	1.06
FD&C Blue No. 1	0.66
FD&C Blue No. 2	-0.32
FD&C Green No. 3	-3.22
FD&C Red No. 40	-0.55
FD&C Yellow No. 5 (tartrazine)	-10.17
FD&C Yellow No. 6 (sunset yellow)	-1.18
Carmoisine	0.00
Ponceau 4R	1.63
Flavors	
Aspartame	0.07
L-Glutamic acid	-3.69
Saccharine	0.91
Preservatives	
BHA	3.50
BHT	5.10
TBHQ	2.94

preservatives are all lipophilic. It is suggested here that some of the conflicting results regarding the neurotoxic effects of artificial food colors may be due to the presence or absence of lipophilic preservatives which facilitate the absorption of the hydrophilic colors and flavors. The Feingold diet, which prescribes the elimination of all synthetic food additives, is devoid of the synthetic lipophilic and hydrophilic xenobiotics.

Further complicating the neurotoxicity of artificial food colors is the fact that the U.S. FDA allows these to be contaminated with neurotoxic heavy metals [33]. The standards for these are:

Lead	not more than 10 ppm.
Arsenic	not more than 3 ppm.
Mercury	not more than 1 ppm.

These metals are all hydrophiles and though their allowable quantities are low, they may nevertheless form neurotoxic mixtures with lipophilic species from other dietary items and have toxic impact. No studies have yet been carried out on the allowable levels of these heavy metals in dietary mixtures containing colors, flavors, and preservatives. A search of the literature did not reveal that any studies related to the Feingold diet analyzed for or considered the effects of lead, arsenic, and mercury.

A further search of the literature did not reveal any research into the effects of exposure to chemicals or chemical mixtures other than synthetic colors, flavors, and preservatives on ADHD. To date, no work has been published on the effects of maternal exposure to colors, flavors, and preservatives.

21.5 Summary

Little is known about the cause of ADHD and no cure has been found for it. It has been shown that maternal ingestion of lead or ethanol as well as smoking or marijuana use are causative agents for ADHD. Both tobacco and marijuana smoke are complex mixtures of thousands of individual chemicals, and the chemical(s) responsible for inducing ADHD have not been identified. It has also been shown that exposures to mixtures of artificial colors and flavors are synergistically neurotoxic.

Though ADHD cannot be cured, the removal of artificial colors, flavors, and preservatives has been demonstrated definitively to reduce ADHD symptoms in as many as half of the children stricken with it and that challenges with these chemicals induce hyperactivity in many children. It is suggested that mixtures of hydrophilic artificial colors and flavors mixed with lipophilic preservatives may be at least partially responsible for the hyperactivity induced in many children who consume such mixtures.

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22 Endocrine System

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22.1 Introduction

The endocrine system is composed of a network of hormone-producing glands that synthesize and release carefully measured doses of these hormones, which in some instances are in the parts per trillion range. Insufficient as well as excessive quantities of these hormones can be detrimental to one's health and well-being. As was discussed in Section 4.11, EDCs are exogenous chemicals that alter the function of the endocrine system by one of the following four different ways:

1. Acting as hormone mimics, i.e., attaching themselves to hormone receptor sites and mimicking the effects of endogenous hormones.
2. Antagonizing the effects of endogenous hormones.
3. Disrupting the synthesis and/or metabolism of endogenous hormones.
4. Disrupting the synthesis and metabolism of endogenous hormone receptors.

Endocrine disrupting chemicals are known to adversely affect the human reproductive process, by impacting both male and female fertility [1–12]. This subject will be examined in Chapter 23. EDCs also affect the thyroid. Thyroid hormone is well known to be essential for brain development, which is sensitive to both thyroid hormone deficit and excess. EDCs affect the thyroid gland and through this action fetal brain development [13–19]. The hypothalamic–pituitary–adrenal axis (HPA axis), a complex interaction between the hypothalamus, the pituitary gland, and the adrenal gland, is a major part of the neuroendocrine system that regulates digestion, the immune system, mood, sexuality, and energy usage. Xenobiotics that disrupt any part of this vital axis can have serious and even catastrophic effects on those so affected [11, 17, 20–25]. There is also suggestive evidence that EDC exposures are responsible for the onset of type-2 diabetes, cardiovascular disease, and breast cancer [26, 80].

Table 22.1 Partial List of Endocrine-Disrupting Chemicals

Alachlor	Formaldehyde
Aldicarb	Heptachlor
Aldrin	Hexachlorobenzene
Ammonium perchlorate	Hydrazine
Arsenic	Hydrogen cyanide
Atrazine	Lead
Benzene	Lindane
Bis(2-ethylhexyladipate)	Malathion
Bis(2-ethylhexylphthalate)	Maneb
Bisphenol A	Mercury
2-Bromopropane	Methoxychlor
Cadmium	Methylene bromide
Carbon disulfide	Mirex
Carbon tetrachloride	Nitrogen dioxide
Chlordane	<i>p</i> -Nonylphenol
Chloroform	Parathion
Chlorpyrifos	PCP
2,4-D	Permethrin
DDE	PBBs
DDT	PCBs
1,2-Dichlorobenzene	Styrene
1,2-Dichloropropane	2,4,5-T
Dibutyl phthalate	TCDD
Dieldrin	Tetrahydrofuran
Diethyl phthalate	Thiocyanate
DES	Tributyltin
Endosulfan	TCE
Epichlorohydrin	Triphenyltine
Ethanol	VM&P naphtha
Ethyl benzene	

22.2 Endocrine-Disrupting Chemicals

A large number of individual chemicals have been demonstrated to be endocrine disruptors. EDCs include pesticides, synthetic hormones, heavy metals, plasticizers, and other industrial chemicals. Table 22.1 contains a partial list of these culled from a number of literature sources [3, 4, 27, 28].

Chemicals toxic to the endocrine system can disturb its development as well as the development of organs that respond to endocrine signals. The damage to the developing organism can occur during prenatal or early postnatal life from exposures both during pregnancy and after birth. In addition, due to the persistence of ED chemicals in body fat, exposures to the mother at any time during her life can result in transgenerational exposures to her offspring via DNA modification [26, 29–31].

Table 22.2 List of Synthetic Estrogen-Mimicking Compounds

Chemical	References
Bisphenol A	[32–35]
<i>p</i> -Nonylphenol	[36]
PCBs	[37, 38]
Phthalate ester plasticizers	[39]
BHA	[39]
BHT	
<i>n</i> -Butylbenzene	[39]
<i>p</i> -Cresol	[39]
2,4-Dichlorophenol	[39]
<i>p</i> -Hydroxybenzoic acid	[39]
DDT	[40]
Kepone	[40]

In keeping with the stated purpose of this book, the endocrine-disrupting effects of single chemicals will be discussed briefly and serve as an introduction to a discussion of the endocrine toxic effects of chemical mixtures.

A number of structurally different xenobiotic chemicals are estrogen mimics. These compounds include pesticides, industrial chemicals, and components of many plastics, including polystyrene and polycarbonate. Some are listed in Table 22.2.

Some xenobiotics have androgenic as well as estrogenic activity. These include phthalate ester plasticizers [41–43], bisphenol A [44], the DDT metabolite DDE [45], and cadmium, a component of cigarette smoke [46, 47]. The effects of these endocrine disruptors include early puberty [48] and male reproductive organ disorders including decreased penis size [42, 43] and hypospadias, the result of arrested development of the urethra, foreskin, and ventral surface of the penis where the urethral opening may be anywhere along the shaft, within the scrotum, or in the perineum [49, 50]. It has been suggested that endocrine disruptors are at least partially responsible for the decreases in human semen quality and quantity [5]. The implications of these effects on infertility will be discussed in Chapter 23.

Ethanol has been shown to induce oxidative damage in the pituitary gland and contribute to pituitary dysfunction. Chronic exposure of laboratory animals to ethanol results in a decline in serum testosterone and decreased serum luteinizing hormone and follicle-stimulating hormone [51].

Drinking-water contamination with endocrine disruptors has become a serious concern. Arsenic, which is a worldwide drinking-water contaminant, is a potent endocrine disruptor [52, 53]. Organochlorine and other endocrine-disrupting persistent organic-polluting chemicals make their way into drinking water and raise questions about water potability in many areas [28]. It has been recently shown that endocrine-disrupting chemicals are transferred from the plastic PET containers used for mineral water to the water. This leads to three times higher estrogen activity in water bottled in a plastic containers than in the same water bottled in glass [54].

It has long been known that hypothyroidism leads to retardation and other serious developmental disorders [15]. It has been shown that the neuropsychological development of a fetus is adversely affected when thyroid deficiency occurs in a pregnant woman and her fetus [55]. Even very small reductions in thyroid levels in mothers during pregnancy have been shown to impact the intellectual levels of children. Free hormone thyroid levels circulating in pregnant women are in the parts per trillion range and thyroid-disrupting chemicals that reduce the hormonal levels even slightly can have huge neurotoxicological effects on the developing fetus. PCBs and the pesticides aminotriazole, dimethoate, and fenvalerate inhibit the release of thyroid hormone. Phthalates and other widely used chemicals compete for sites on the thyroid transport proteins that deliver thyroid hormones throughout the body [56]. It has been suggested that thyroid-disrupting xenobiotics may be related to increases in the prevalence of autism and ADHD, though this has not, to date, been proven [56].

22.3 Diabetes and EDCs

Diabetes is a disease that ensues when the body fails to produce or use insulin appropriately. This disease currently affects more than 6% of the U.S. population (21 million people). The International Diabetes Federation (IDF) estimates that there are 246 million people with diabetes worldwide in 2007 compared with 194 million in 2003. The following IDF data indicate the scope of the worldwide diabetes epidemic [57]:

Year	Millions of diabetics
1985	30
2000	150
2025	380 (estimated)

Diabetes is primarily concentrated in urban areas and is most prevalent in people who are obese, eat an unhealthy diet, and live sedentary lifestyles. The highest diabetes prevalences are in North America (9.2%) and Europe (8.4%) [57].

The most prevalent form of diabetes, which accounts for 85–95% of all cases, is type-2 diabetes, defined by reduced insulin production and insulin resistance. Insulin resistance occurs when increasing quantities of insulin are required to regulate the transport of plasma glucose to body tissues. It is often accompanied by obesity, which elevates the free fatty acid levels in blood serum and is thought to induce insulin resistance [58].

Recent research into the biology of adipose tissue has revealed that adipose is not simply an energy storage site, but that it also secretes a variety of molecular species that affect the body's metabolism. Adipocytes are cells contained in adipose tissue that have been shown to be endocrine cells that secrete a number of bioactive substances called adipocytokines. The adipocytokines include adiponectin, a protein that is an insulin-sensitizing hormone [59, 60]. The secretion of virtually all known

adipose proteins is reduced when white adipose tissue (WAT) mass is markedly increased, as in the obese. Adipose protein secretion is also markedly reduced when WAT is markedly decreased, as in liposuction [61]. Levels of adiponectin mRNAs and its plasma levels are reduced in obesity and in type-2 diabetes [59, 60, 62, 63].

With the knowledge that adipose tissue is an endocrine organ, it is suggested that it may be impacted by endocrine-disrupting chemicals and be a causative effect for type-2 diabetes. This connection is advanced by the following four-point argument [58]:

1. Testosterone is known to affect body fat distribution and insulin sensitivity in men. Testosterone administration has been shown to reduce total fat mass and improve insulin sensitivity [64].
2. Humans are constantly exposed to synthetic chemicals that are antiandrogenic. These chemicals include phthalates, which are used in a wide variety of products including prescription drugs, cosmetics, soaps, shampoos, adhesives, paints, lubricants, and as a plasticizer for PVC [65]. Even though phthalates (with half-lives of less than 24h) are rapidly metabolized by humans, more than 75% of the people in the United States have measurable quantities of several phthalate metabolites in their urine [66].
3. Antiandrogenic effects have been associated with several phthalates [67], as well as with PCBs, dioxins, and organochlorine pesticides, chemicals which have been associated with diabetes prevalence in adult men [68, 69]. Mixtures of phthalates and other antiandrogens have been shown to act in an additive manner in animal studies [70, 71], and in a greater than additive manner in one human study [72].
4. The Stahlhut, van Wijngaarden, and Dye study [58] found that there is a correlation between urinary phthalate metabolite concentrations and abdominal obesity and insulin resistance in men. It is suggested that the antiandrogenic phthalates adversely impact testosterone production, which in turn results in obesity and insulin resistance, both of which are related to type-2 diabetes. Though the authors do not discuss the effects of phthalates or other antiandrogens on adipocytes, it is thought that such an effect may also play a role in the onset of type-2 diabetes. The mechanism(s) operating remain unknown, but it is known, however, that WAT is a repository for numerous lipophilic POPs, including PCBs, dioxins, DDT, DDE, and other organochlorine pesticides and that these chemicals are endocrine disruptors [73]. Unlike phthalates, which are fairly rapidly metabolized, these POPs metabolize very slowly (with half-lives of years). The effects of the interactions of the POP metabolites with other xenobiotics and their effects, if any, on diabetes remain areas of ongoing research.

Though it is tempting to attribute the epidemic increase in diabetes in the last two decades to the ubiquitous phthalates, more research remains to be carried out before this is proven. The Stahlhut, van Wijngaarden, and Dye [58] study correlates urinary phthalate metabolite presence with insulin resistance only. The connection to type-2 diabetes has thus been suggested but proof awaits further inquiry. There is new evidence, however, that exposure to POPs commonly found in food chains leads to insulin resistance and associated metabolic disorders [62, 63].

22.4 Breast Cancer and Endocrine Disruptors

It has been shown that environmental toxicant exposure during rapid growth and differentiation is associated with increased susceptibility to cancer. Prenatal human exposure to ionizing radiation is known to increase cancer rates, and there

is suggestive evidence that leukemia and brain cancers are associated with parental exposures to chemicals [74, 75, 80]. It is also known that prenatal exposure to natural and synthetic estrogens is associated with increased breast and vaginal tumors in humans and that TCDD, an endocrine-disrupting chemical, has been shown to adversely affect mammary gland development in laboratory animals [74].

Other environmentally pervasive xenoestrogenic chemicals have also been associated with human breast cancer. The connection between xenoestrogenic exposure and human breast cancer is a circumstantial one. It is based on the following nine parameters:

1. Parabens, which are used as preservatives in a multitude of food, cosmetic, and pharmaceutical products, have been shown to exhibit estrogenic properties and to accumulate chemically intact in human breast tissue [76].
2. Fetal exposure of mice to low doses of bisphenol A results in mammary gland effects, including neoplasias that are manifested in adult life [77, 78]. Both bisphenol A sulfate and bisulfate have been shown to stimulate the growth of receptor-positive breast tumor cells [79].
3. Exposure to excess estrogen is believed to be associated with an increased risk of developing breast cancer [77, 80, 81]. The continuing rise in breast cancer incidence rates in the Western countries cannot be entirely explained by genetic risk factors alone and it is estimated that 90% of breast cancers are due to environmental exposures [82]. Elevated levels of endogenous estrogen and its use by women for alleviation of menopausal symptoms has been associated with increases in breast cancer rates [80, 81]. Chlorinated hydrocarbon pesticides, BCBs, dioxins, phthalates, bisphenol A, nonylphenol, aluminum chlorohydrate, BHA, BHT, and triclosan are some of the chemicals that are widely used and widely distributed in the environment that are estrogenic.
4. The compounds that have been identified as xenoestrogens vary widely in chemical nature. Many are highly lipophilic and slowly metabolized (TCDD, chlorinated hydrocarbon pesticides). Others are less lipophilic and more labile (phthalates) and some are hydrophilic (methylparaben, aluminum chloride, and aluminum chlorohydrate). It is known that lipophilic chemicals are more readily absorbed through the skin than hydrophilic chemicals, but as has been pointed out repeatedly in this book, lipophiles facilitate the absorption of hydrophiles and contribute to unexplained mixture effects. Table 22.3 lists some of the known xenoestrogens, types of products they are used in, and their K_{ow} values.
5. Because studies have shown that these estrogen-like chemicals are weakly estrogenic compared with endogenous hormones, there has been a tendency to dismiss their impact. Recent studies, however, have demonstrated that mixtures of these, each at the NOEC, dramatically enhance hormone action [83, 84]. In these studies, the mixtures of xenoestrogens contained compounds commonly found in foods, cosmetics, sunscreens, plastics, and in the extended environment. It is significant to note that in both studies, the mixtures were composed of chemicals that were dissimilar structurally and chemically from each other. Seemingly, the only shared characteristic was estrogenic activity. One of the studies [83] included hydroxylated PCBs, benzophenones, parabens, and bisphenol A.
6. The role of cosmetics in promoting the onset of breast cancer has received considerable attention. Xenoestrogens from environmental sources (PCBs and organochlorine pesticides) have been found in breast adipose tissue and in human breast milk. The breast, however, is also exposed to xenoestrogens that are applied topically to underarms and breast skin [81, 85]. These include:

Parabens

Aluminum salts

Table 22.3 Xenoestrogenic Compounds, Products They are Used In, and Their K_{ow} Values

Compound	Use	K_{ow}
Bis(2-ethylhexyl)phthalate	Plastics	7.60
Dibutyl phthalate	Plastics	4.50
Monobutyl phthalate	Cosmetics, cleansers	2.84
DDT	Pesticide	6.91
DDE	Pesticide metabolite	6.51
Endosulfan	Pesticide	3.83
Chlordane	Pesticide	6.16
Methoxychlor	Pesticide	5.08
Dieldrin	Pesticide	5.20
Heptachlor	Pesticide	6.10
Mirex	Pesticide	7.18
Triclosan	Cosmetics	4.76
TCDD	Pesticide impurity	6.80
BHA	Food preservation	3.50
BHT	Food preservation	5.10
PCBs	Dielectric fluid	6.29–7.65
Methyl paraben	Cosmetics	1.96
<i>n</i> -Butyl paraben	Cosmetics	3.57
Bisphenol A	Plastics	3.32
Nonylphenol	Surfactants	5.76
2,4-Dihydroxybenzophenone	Sunscreens	3.69
Octyldimethyl- <i>p</i> -aminobenzoic acid	Sunscreens	5.77
Aluminum chloride	Antiperspirants	1.26
Aluminum chlorohydrate	Antiperspirants	−0.30

Cyclosiloxanes

Triclosan

UV light absorbers

Phthalates

Anthraquinones

Nonylphenol.

All of these compounds are readily absorbed through the skin in the breast area. Because they are not ingested or inhaled, they are not subjected to metabolism, but arrive at and are stored in breast adipose intact [81].

7. The strongest evidence supporting the hypothesis that xenobiotics in underarm cosmetics are a cause of breast cancer comes from clinical observations showing disproportionately high incidences of breast cancer in the upper–outer quadrant of breast. This corresponds to the area where deodorants and other cosmetics are applied [86–88].
8. More suggestive evidence for the connection between cosmetic use and breast cancer comes from a consideration of breast cancer rates in pre-menopausal women. Evidence for this hypothesis comes from a comparison of breast cancer rates in African-American and Caucasian women in the United States. Breast cancer rates in African-American women are higher than those for Caucasians, as is their use of xenoestrogen-containing personal care products [89].
9. The association between obesity and insulin resistance as risk factors for breast cancer provides still more suggestive evidence. As was seen in the earlier section, obesity and insulin

resistance are influenced by EDCs. Obesity is related to increases in adipocytokine production and some of these polypeptides promote angiogenesis (the process of developing new blood vessels), which is essential for breast cancer development and progression. Experimental evidence also exists showing that some adipocytokines act directly on breast cancer cells and stimulate their proliferation and invasive capacity. Thus it is hypothesized that adipocytokines may play a role in causing breast cancer [90].

Though the circumstantial evidence is strongly suggestive, to date there is no proven link between the presence of these xenoestrogens in breast tissue and the onset of breast cancer. It is possible that these chemicals act additively or even synergistically with other xenoestrogens to promote breast cancer. Research in this area is ongoing.

Finally, it should be noted that smoking, both active and passive, has been associated with breast-cancer risk [91]. Tobacco smoke contains cadmium, a known endocrine disruptor, as well as numerous carcinogens. No mechanism has yet been proposed for the association between smoking and breast cancer.

22.5 Mixture Effects on Endocrine Function: Case Studies

Mixtures of endocrine-disrupting chemicals have been shown to produce additive, synergistic, and unexpected dose-response effects. The following studies are illustrative of the effects noted:

1. Linuron, a urea-derivative herbicide and androgen-receptor antagonist, and butyl benzyl phthalate, a plasticizer, are two compounds with very different chemical properties, yet in a laboratory animal study, prenatal exposure to a mixture of these produced dose-additive testosterone and other adverse developmental effects [70].
2. In an in vitro study, mixtures of six synthetic endocrine-disrupting chemicals and plant-derived phytoestrogens were evaluated for estrogenic activity. The EDCs were:

Methoxychlor

o,p-DDT

Octylphenol

Bisphenol A

Beta-hexachlorocyclohexane

2,3-Bis(hydroxyphenyl)-propionitrile.

At low doses, additive effects were observed. At higher doses, however, the responses of mixtures of synthetic EDCs and phytoestrogens were greater than additive. In this study, mixtures of the synthetic chemicals alone interacted in a less than additive manner [92]. These results illustrate the often unpredictable interaction of endocrine-disrupting mixtures.

3. An in vitro study of ternary mixtures of xenoestrogens demonstrated that additive effects of EDCs are often observed when the chemicals that comprise the mixture are similar and that different effects may be observed when the chemicals are different. In this study, the following three mixtures were prepared and evaluated for estrogenic activity:

(a) Methoxychlor,
o,p-DDT,
Dieldrin

(b) Benzo[a]pyrene,
1,2-Benzanthracene,
Chrysene

(c) 17-Beta-estradiol, Genestein
(a phytoestrogen),
o,p-DDT

Additive effects were observed for the organochlorine pesticide mixture (a) and the mixture of polyaromatic hydrocarbons (b). The mixture of the natural hormone, the phyto-hormone, and the organochlorine hydrocarbon (c), however, exhibited an antagonistic response [93].

4. In an "in culture" bioassay using human-breast estrogen-sensitive MFC7 cells to assess the estrogenicity of several pesticides, it was found that mixtures of the pesticides induced estrogenic responses at lower concentrations than those required for the single pesticides. The pesticides tested included DDT, chlordecone, dieldrin, toxaphene, and endosulfan [94].
5. UV filters are formulated into sunscreens and cosmetics to protect against solar UV radiation, and commercial sunscreen and cosmetic products often contain mixtures of these filters. Eight different UV filter compounds were tested in mixtures of two, four, and eight alone or combined with 17-beta-estradiol for estrogenic activity in a recombinant yeast assay carrying the human estrogen receptor alpha. Despite the concentrations of all compounds being at the NOEC levels, most binary mixtures and all four- and eight-component mixtures showed synergistic activity [95]. These results demonstrated the difficulties encountered when trying to predict the endocrine toxicology of mixtures based upon the known toxicities of single chemicals.
6. Many single endocrine-disrupting chemicals are known to be toxic to the HPT axis. Studies with sexually mature male laboratory animals, however, have indicated that the toxicities to the HPT axis demonstrated by the individual chemicals are manifested only at levels much higher than those humans are commonly exposed to environmentally. A study of the combined effects of a mixture of common organochlorine pollutants and heavy metals demonstrated that the mixture impacted thyroid endpoints, including circulating thyroid hormone levels and thyroid physiology, in test animals, when each was present at very low concentration, i.e., at minimum risk or daily tolerable levels. The chemicals in the mixture were:
 - DDT
 - DDE
 - TCDD
 - PCBs
 - Methoxychlor
 - Endosulfan
 - Heptachlor
 - Hexachlorocyclohexane
 - Dieldrin
 - Aldrin
 - Mirex
 - Several chlorinated benzenes
 - Lead
 - Cadmium.

The authors of the study concluded that low doses of ubiquitous environmental pollutants can alter HPT physiology in sexually mature males [96].

7. A study was designed to test the mixture effects of different concentrations of known thyroid-disrupting chemicals. The mixture consisted of several each of dioxins, PCBs, and PDBE. The study tested the concentrations of serum total thyroxine (T4) following administration to laboratory animals at different concentrations, ranging from environmentally found background levels to 100 times those levels. The ratio of chemicals was based on environmental concentrations. The results showed that additive effects were obtained at

lower concentrations, but that synergistic effects prevailed at higher concentrations, with (T4) levels dropping by two to three times predicted levels [97].

8. Ammonium perchlorate and sodium chlorate are common water pollutants in some areas of the United States. Each affects the pituitary–thyroid homeostasis by inhibiting iodine uptake, thus interfering with the synthesis of thyroglobulin and reducing circulating thyroxine. The administration of low levels of ammonium perchlorate and sodium chlorate alone did not reduce circulating thyroxine levels in laboratory animals. Thyroxine levels, however, were significantly reduced when the same levels of these chemicals were administered as a mixture [98]. This study pointed out the danger posed when both compounds are present in drinking water.
9. Endocrine-disrupting chemical contaminants in drinking water are typically removed by treatment with UV radiation and hydrogen peroxide. In an EDC removal study, mixtures of four EDCs were prepared in laboratory water and in natural river water to evaluate the efficacy of UV/hydrogen peroxide treatment. The EDCs included estradiol, ethinyl estradiol, bisphenol A, and nonylphenol. Treatment success was evaluated by testing for estrogenic activity *in vitro* (yeast estrogen screen) and *in vivo* (with fish). Typical treatment levels of UV and peroxide successfully removed all estrogenic activity *in vitro*, but not *in vivo*. Estrogenic activity removal rates were higher in laboratory water than in natural river water. The authors attributed this difference to the presence of radical scavengers in river water [99]. These results are indicative of the sensitivity of living organisms to very low levels of endocrine disruptors and the need to carefully test the effects of EDCs under all conditions of exposure.

22.6 Tobacco Smoke

Tobacco smoke is a complex mixture of more than 4000 different chemicals that has multiple toxic effects on the endocrine system. In addition to the associations between tobacco smoke and breast cancer (Section 22.4), smoking has other endocrine-disrupting effects. Smoking affects the pituitary, thyroid, and adrenal glands, and the testes and ovaries. It also affects the action of insulin and smoking is believed to be a causative agent for diabetes [100]. Cigarette smoke contains compounds suspected of causing reproductive damage by affecting steroidal hormones [101], and parental smoking also affects thyroid function in infants [100]. Though nicotine is believed to be responsible for some of these effects, others have so far defied explanation. The complexity of tobacco smoke makes identification of the responsible endocrine-disrupting chemicals difficult to ascertain, though it is thought that smoking leads to an increased risk of pancreatitis [102]. To date, there have not been any published studies that address the combined effects of known EDCs and tobacco smoke. The reader is referred to literature for an excellent review of the state of knowledge regarding the toxic effects of tobacco smoke to the endocrine system [100].

22.7 Summary

Endocrine-disrupting chemicals can wreak havoc with the human reproductive process as well as with endocrine system homeostasis. Their introduction into the

environment has had an enormous effect on wildlife. Given the similarities between many of the hormones (particularly the sex hormones) that circulate in animal and human bodies, the wildlife impacts serve as models and predictors of the effects of EDCs on humans.

Mixtures of EDCs have been shown to exhibit low-level and unexpected endocrine effects, even at NOEC levels, and have been strongly identified with type-2 diabetes and breast cancer in women. Though definitive proof of these associations is still awaited, it should not be surprising if EDCs were connected with other “mysterious” illnesses in the future.

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23 Toxic Infertility

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23.1 Introduction

Toxic infertility as used here refers to adverse effects on the reproductive systems of human males and females that result from exposure to xenobiotic single chemicals and chemical mixtures. This infertility may be due to direct toxic effects on the male or female reproductive organs and endocrine systems, or on the developing fetus such that the fetus either cannot be conceived or cannot be carried to term after conception. Developmental toxicity, the onset of adverse effects on the developing fetus or child after birth, will be discussed in Chapter 24.

Reproductive disorders in humans are known to be caused by more than 100 different individual chemicals and suspected to be caused by some 200 more. Table 23.1 lists some of these compounds and their K_{ow} values [1]. As can be seen from this table, many different types of chemicals containing far different functional groups cause reproductive disorders. These include aliphatic and aromatic hydrocarbons, glycol ethers, chlorinated hydrocarbons, pesticides, and heavy metals [2]. Both lipophilic and hydrophilic compounds are contained on the list. Some of the chemicals are rapidly metabolized, while others accumulate in adipose tissue and are stored in the body for long periods of time. The mechanisms by which many of these chemicals act remain unknown.

Products containing infertility causative agents include adhesives, paints, silicones, solvents, and the fumes from welding rods that emitted during welding [3]. House dust containing organophosphate flame retardants has been shown to alter hormone levels and decrease sperm quality in men [4].

Infertility rates in both women and men have been continually rising. It is estimated that approximately 50% of human conceptuses fail to reach term. Sperm count in men has been continually declining over the past 50 years. At the same time increases in hypospadias, cryptorchidism, and testicular cancer have further contributed to increasing male infertility. Xenoestrogens have contributed to male and female infertility. SAB rates and preterm births continue to rise, contributing further to infertility.

Xenobiotic chemicals are thought to contribute to all these causes of infertility, though the effects of chemical mixtures on infertility have only recently begun to be explored [5]. This chapter will examine the effects of chemical mixtures on female and male infertility from the perspectives of the impacts on exposures by adults as well as by fetuses.

23.2 Xenobiotics and Female Infertility

Xenobiotic exposures can impact female fertility in humans in several ways. Much of the published research on xenobiotic impact on female infertility has concerned itself with the effects of pesticides [6]. The effects, however, are just as applicable to other toxicants. Interference with any of the following six processes adversely impacts fertility:

1. *Hormone synthesis*: All hormones vary in chemical structure. Each is made via a multistep synthesis, every step of which can be impacted by xenobiotics.

Table 23.1 Single Chemicals Known (K) or Suspected (S) to be Reproductively Toxic Chemicals

Acrylamide	-0.69	S
Acrylonitrile	-0.34	S
Aldicarb	1.13	S
Aldrin	6.50	S
Aluminum chloride	1.26	S
Arsenic	0.68	S
Benzene	2.13	K
1-Bromopropane	2.10	S
1,3-Butadiene	1.99	K
2-Butoxyethanol acetate	1.57	S
Cadmium	-0.07	K
Carbon disulfide	1.94	K
Carbon tetrachloride	2.83	S
Chlordane	6.16	S
Chloroform	1.97	S
2,4-D	2.81	S
DDT	6.91	K
Dibromochloropropane	2.30	K
Dibutyl phthalate	4.50	S
Dinitrotoluene	2.18	K
Epichlorohydrin	0.45	K
Ethanol	-0.31	S
Ethylene dibromide	1.96	K
Ethylene glycol	-1.36	S
Ethylene glycol monobutyl ether	0.83	S
Ethylene glycol monoethyl ether	0.32	K
Ethylene glycol monoethyl ether acetate	0.59	K
Ethylene oxide	-0.30	K
Formaldehyde	0.35	S
Lead	0.73	K
Methylene chloride	1.25	S
MEK	0.29	S
Methyl isocyanate	0.79	S
Methyl methacrylate	1.38	S
Toluene	2.73	S
TCE	3.40	S
VC	1.62	S
Xylene	3.15	S

2. *Hormone transport:* Steroid hormones bind to carrier proteins and are transported in the bloodstream to their required sites. At these sites, the hormones transfer to storage sites where they await release for use. When these carrier proteins are interfered with, the hormones are not delivered to required sites.
3. *Hormone storage and release:* For a woman to be fertile, hormones must be stored and available for release at the precise time of need. Chemicals that block the storage sites or prevent their release once stored interfere with hormone availability.

4. *Hormone receptor recognition and binding:* Hormones convey messages to particular tissues by binding to receptors. Hormone mimics are chemicals that interfere with this process. Agonists act by binding to hormone receptor sites. Antagonists inhibit receptor binding. Both adversely impact the initiation of steps required for fertility.
5. *Thyroid function:* Some xenobiotics reduce the quantities of circulating thyroid hormone levels. This can result in altered hormone metabolism.
6. *CNS function:* The CNS is critical in the integration of behavior with hormonal activity. Some neurotoxins disturb normal behavior and the reproductive process.

Pesticides have been shown to impact every one of the six processes listed earlier. Since pesticide residues are ubiquitous in the human environment and food supply worldwide (see Chapter 10), fertility declines should not be surprising. An excellent review of the subject is contained in a recent paper by Bretveld et al. [6].

Though no pesticide or other chemical impacts all six processes, it is very clear that simultaneous exposures to multiple pesticides can have greater effects than those expected from exposures to single pesticides alone. For example, alachlor and atrazine are two herbicides that are applied together to cornfields in Nebraska [7]. Alachlor binds to and activates the estrogen receptor [8]. Atrazine interferes with hormone synthesis [9]. In the Nebraska study cited, the two herbicides were also mixed with seven other pesticides and induced reproductive effects in reptiles far in excess of those predicted by a consideration of the individual species [7].

Some chemicals can have multiple effects on fertility. Alkaloids in cigarette smoke, nicotine, cotinine, and anabasine, when administered alone or as a mixed aqueous extract of cigarette smoke, for example, inhibit progesterone synthesis and have a cytotoxic effect that reduces the fertilization, implantation, and embryonic viability [10–12].

Some chemical exposures and employment in some occupations where chemicals are used are known to impact fertility in women. These include exposures to lead, manganese, organic mercury compounds, carbon disulfide, 2-bromopropane, and welding fumes [13].

23.3 Smoking and Female Fertility

It has been shown that women exposed to cigarette smoke as well as those with pre-natal exposures to their mothers' cigarette smoke have substantially less fecundity (the ability to produce offspring within a given period of time) than women who are not exposed to smoke and whose mothers did not smoke during pregnancy [14, 15].

In a study with donated oocytes, it was shown that women who smoke are less fertile than those who do not and that exposure to tobacco smoke affects uterine receptiveness to embryo implantation [16].

Maternal smoking, even moderate smoking, increases the risk of preterm birth. A laboratory study on animals has shown that exposure to mainstream cigarette smoke at concentrations equivalent to smoking less than one pack of cigarettes per day resulted in a significant shortening of gestation as well as elevated serum estrogen

levels and reduced progesterone to 17-beta-estradiol levels. Anatomical effect differences were also noted [17].

Maternal smoking during early pregnancy has been shown to reduce the number of germ and somatic cells in male and female embryos. The authors of the study concluded that this may influence the future fertility of exposed offspring [18].

Smoking also interferes with fertility by altering the menstrual cycle. Acting through some unknown mechanism, it was demonstrated via steroid hormone metabolites in women that tobacco smoke contributed to variable cycle lengths, with shortening of the cycle being the primary effect [19]. These effects are consistent with lower fecundity in cigarette smokers than in nonsmokers.

The mechanisms for the effects of tobacco smoke on female fertility remain largely unknown. The transgenerational effect noted [14] is particularly without explanation. As has been previously noted, there are more than 4000 single chemicals in tobacco smoke and the numbers of mixtures possible are endless.

23.4 Chemically Induced SAB

It has been known for some time that there is a positive association between occupational exposures to organic solvents and solvent mixtures and SAB [20]. Studies carried out on three different groups of women with different employment exposures demonstrate this point.

23.4.1 Shoe Industry Employees

A high risk of SAB was reported in female Italian shoe factory employees [21]. Shoe manufacturing requires the use of adhesives that are dissolved in mixtures of lipophilic and hydrophilic organic solvents [22, 23]. The solvents typically used (and their K_{ow} values) are:

<i>n</i> -Hexane	3.90
Cyclohexane	3.44
<i>n</i> -Heptane	4.66
MEK	0.29
Ethyl acetate	0.73

No mechanistic explanation was offered for the observed increases in SAB.

23.4.2 Semiconductor Manufacturing

Women working in semiconductor manufacturing plants that use mixtures containing ethylene glycol ethers have higher SAB rates than women who do not work in these plants [24, 25]. Semiconductor manufacturing plant workers are exposed to

numerous organic solvents including lipophiles and hydrophiles [26]. These chemicals include:

Ethylene glycol monobutyl ether	0.83
TCE	3.40
Hydrofluoric acid	0.23
Nitric acid	0.21
Methylene chloride	1.25
Toluene	2.73

The mechanistic cause for the observed increase in SAB is unknown.

23.4.3 Toluene Mixtures

Though toluene alone is not known to induce SAB, an occupational study in Finland has reported associations when pregnant women were exposed to mixtures of toluene with other organic solvents, including hydrophilic and lipophilic species [27]. These studies point out difficulties encountered where adverse health associations are made without considering mixture effects.

23.4.4 Agricultural Mixtures

Occupational exposures to pesticides are believed to increase SAB rates. In a study on laboratory mice, the animals were exposed to a low-dose mixture of herbicides, insecticides, a desiccant, and a fertilizer, a combination commonly used in the upper Midwestern United States. The chemicals contained in the mixture were:

Atrazine	2.61
Dicamba	2.21
Metolachlor	2.90
2,4-D	2.81
Pendimethalin	2.34
Mecoprop	3.13
Chlorpyrifos	4.96
Terbufos	4.48
Permethrin	6.50
Diquat	2.36
Ammonium nitrate	-4.39

Mixtures simulating groundwater pollution were administered to the test animals. The mixture reduced development to blastocyst and mean cell number per embryo, simulating what is expected in SAB [28]. The authors of the study concluded that these results demonstrate that agricultural mixtures can induce early development effects at concentrations assumed to be safe for human consumption.

23.4.5 Anesthetic Gases

It has been known for some time that anesthetists, other operating room personnel, dentists, and dental associates have higher rates of SAB and other adverse birth outcomes than control groups [29–31]. The chemicals these women are exposed to include halothane, nitric oxide, methoxy flurane, and other unspecified chemicals from antiseptic solutions, propellants, and adhesive solutions [29]. Symptoms reported by these workers include headache and nausea effects that are indicative of CNS impact. These effects are consistent with those expected from anesthesia and are indicative of the impact of neurotoxins on fertility.

23.4.6 Laboratory Workers

Pregnant women who work in chemical laboratories have higher rates of SAB than those who do not. Two studies demonstrated this point. In the first, women working in Swedish pharmaceutical chemical laboratories were found to have significantly higher rates of SAB than women working in other laboratories in the same facilities [32]. In a second study, it was found that pregnant women who worked in pulp and paper mill laboratories had higher SAB rates than those who worked in other areas of these plants [33]. The exposures in both studies were to organic solvents and other chemicals.

23.4.7 ETS Exposure

Nicotine in tobacco is metabolized to cotinine and urinary cotinine levels serve as indicators of the levels of exposure to ETS, also referred to as secondhand smoke. In a Swedish study, a relationship between increased urinary cotinine level and increased risk for SAB was demonstrated [34]. No specific chemical(s) were identified as the causative agent(s).

23.4.8 Marijuana Use

In a laboratory study on mice, a component of marijuana has been shown to cause early pregnancy failure in mice by blocking binding sites and preventing implantation of the embryo in the uterus. THC, the major psychoactive component of marijuana, has been shown to be the responsible agent [35]. Marijuana, the most widely used psychoactive drug, thus presents a formidable barrier to fertility. It should be noted that smoking marijuana also exposes one to numerous other toxic compounds, as in smoking tobacco.

23.4.9 Formulated Pesticide Use

Glyphosate is a herbicide used worldwide to control unwanted plant growth. Roundup is a common herbicide product that is glyphosate-based and formulated with other chemicals to facilitate its action. In a study designed to examine the toxicity of glyphosate and Roundup to human placental JEG3 cells, it was found that

glyphosate is toxic to these cells and that Roundup reduces JEG3 cell viability at least twice as much as glyphosate alone. It was further found that Roundup reduces cell viability to the same extent as glyphosate alone at concentrations 10 times lower than glyphosate alone [36]. The authors of the study concluded that the adjuvants in Roundup facilitate the absorption of glyphosate through the cell membrane and hence the greater toxic effect. This is consistent with the finding that lipophiles (such as those contained in Roundup) facilitate the absorption of hydrophiles (such as glyphosate, with a K_{ow} of -4.00).

23.4.10 Water DBPs

As discussed in Section 8.9, disinfection of drinking water with chlorine gives rise to DBPs. Several studies have shown that drinking cold tap water containing DBPs is associated with increased incidence of SAB in a dose-related manner [37–40]. One study, for example, found that SAB was doubled in women drinking six or more glasses of cold tap water per day compared with women not drinking any tap water [37].

Most studies that examined the relationship between DBPs and SAB related the rates of SAB with total THMs, the principal DBPs, and the ones subject to EPA regulation [41]. One of the studies found a relationship between elevated rates of SAB and drinking tap water with bromodichloromethane, one of the THMs, as well as with total THM levels [38]. That study did not, however, find an association between increased SAB and dermal exposure, showering and swimming in THM and bromodichloromethane contaminated water. This is surprising given the propensity for THMs to absorb through the skin [42] and suggests that the toxicity of DBPs, particularly as it pertains to SAB, is complex and requires a consideration of the entire mixture and not just THMs [39, 43]. Table 23.2 contains a comprehensive list of DBPs and their K_{ow} values. The compounds include THMs, HAAs, HANs, and haloketones.

As can be seen from the data, water disinfected with chlorine can contain a complex mixture of lipophiles and hydrophiles. The lipophilic THMs can facilitate the absorption of the hydrophilic HAAs, HANs, and haloketones. An analogy between the reproductive toxicity and carcinogenicity of DBPs can be drawn. Though no single chlorinated by-product studied appears to be carcinogenic, there is evidence from animal studies that DBP mixtures are carcinogenic [44].

23.5 Xenobiotics and Male Infertility

There has been a significant increase in male infertility over the past three-quarters of a century. This time frame corresponds to one where dramatic increases in the use of pesticides and other synthetic chemicals have occurred. Many different chemicals have been associated with male infertility, including pesticides, heavy metals, dioxins, PCBs, phthalates, and others.

Male fertility depends upon normal development during the fetal period and extending through childhood growth and puberty. Xenobiotic exposures after puberty can also affect fertility, an example of which is occupational exposure to chemicals [92].

Table 23.2 DBPs from Chlorination of Drinking Water and Their K_{ow} Values

	K_{ow}
THMs	
Chloroform	1.97
Bromodichloromethane	2.00
Chlorodibromomethane	2.16
Bromoform	2.40
HAAs	
Chloroacetic acid	0.22
Dichloroacetic acid	0.92
TCA	1.33
Bromoacetic acid	0.41
Bromochloroacetic acid	0.61
Dibromoacetic acid	0.70
HANs	
Bromochloroacetonitrile	0.38
Dichloroacetonitrile	0.29
Haloketones	
1,1-Dichloropropanone	0.20
1,1,1-Trichloropropanone	1.12

Male infertility is manifested in several manners. These include sex organ malformation, reduced sperm count, reduced level of seminal fluid, decreased libido, and testicular cancer. Discussions of these conditions, all of which have been attributed to xenobiotic influences (primarily by endocrine disruptors [45]), follow.

23.5.1 Genital Malformations

Genital malformations are the most common birth defects in man [46]. Hypospadias is the result of arrested development of the urethra, foreskin, and ventral surface of the penis where the urethral opening may be anywhere along the shaft, within the scrotum, or in the perineum [47]. Cryptorchidism is the failure of one or both testes to descend into the scrotum. The incidence of both conditions has increased dramatically in recent years and has been associated with in-utero exposures to endocrine-disrupting chemicals [47–50]. Mixtures of pesticides and other estrogenic and antiandrogenic xenobiotics have been causally related to both conditions [48, 50], and maternal consumption of ethanol during pregnancy has been shown to increase the risk of cryptorchidism [51].

23.5.2 Impaired Spermatogenesis

It is estimated that 6% of reproductive age men are infertile and that 90% of those are related to impaired spermatogenesis [52]. It is believed that impaired

spermatogenesis is related to prenatal and neonatal exposures to endocrine-disrupting chemicals [53, 54].

23.5.3 Decreasing Semen Quality

Sperm counts in men have declined by about 50% during the time period 1940–1990, from an average of 113 million per mL of semen in 1940 to an average of 66 million in 1990. During the same time frame there has been a decrease in seminal volume from 3.40 to 2.75 mL [55]. The reasons for the observed decline in semen quality are exposures to pesticide mixtures [56] and other xenobiotic endocrine disruptors [57], maternal consumption of beef containing anabolic steroids [58], and other xenobiotics and tobacco smoking [59].

23.5.4 Testicular Cancer

The incidence of testicular cancer rose sharply in the twentieth century [52]. Because testicular cancer occurs predominantly in younger men (aged 15–19), this increase has contributed to overall male infertility. The steep increase in testicular cancer has been associated with in-utero exposures to endocrine disruptors [60, 61].

23.6 Chemicals Affecting Male Infertility

As discussed earlier, male infertility has been associated with exposures to xenobiotic chemicals. Though effects have been reported for single chemicals, most are based on laboratory testing on animals, since most environmental exposures to humans come from mixtures. Some data, however, have been collected from infertility induced by industrial and environmental exposures. Table 23.3 contains a partial list of chemicals associated with male infertility [52, 62–70]. These chemicals include pesticides, heavy metals, and industrial chemicals.

23.7 Effects of Chemical Mixtures on Male Fertility

Exposures to the chemicals listed in Table 23.3 are rarely to single chemicals. Regrettably, few studies have been carried out on the effects of mixture exposure and male infertility. Those that have addressed this subject have shown that unanticipated effects are indeed encountered. The following illustrate this point.

23.7.1 Organic Solvent Mixtures

Several studies have linked paternal exposure to organic solvents with infertility [71–73]. Two of the studies [74, 75] related the increased infertility with exposures

Table 23.3 Endocrine-Disrupting Chemicals Associated with Male Infertility

Pesticides	Industrial and environmental chemicals
Carbaryl	Aromatic hydrocarbons
Chlordane	2-Bromopropane
1,2-Dibromo-3-chloropropane	Carbon disulfide
Dieldrin	Chloroprene
Difocal	1,2-Dibromo-(1,2-dibromoethyl)cyclohexane
DDE	Dioxins
DDE	2-Ethoxy ethanol
Endosulfan	Ethylene dibromide
Kepone	Methyl chloride
Lindane	Ozone
Malathion	PCBs
Methoxychlor	Phthalates
Mirex	Styrene
Pentachlorophenol	TCE
Toxaphene	VC
Heavy metals	
Aluminum	
Arsenic	
Boron	
Cadmium	
Chromium	
Copper	
Lead	
Manganese	
Mercury	

to mixtures of aromatic solvents (benzene, toluene, and ethyl benzene). One study reported significantly decreased implantation rates after in-vitro fertilization following paternal exposure to unspecified organic solvents [76].

A case-control study of the effects of occupational exposures on male infertility found that a mixture of styrene ($K_{ow} = 2.95$) and acetone ($K_{ow} = -0.24$) affects the male genital system and leads to impotence, infertility, and increased SABs in their wives [77]. Similar effects were reported following workplace exposures to pesticides, heavy metals, and other chemicals. No mechanism(s) for the actions of these chemicals were reported.

23.7.2 Pesticide Mixture

In a study of men living in an agricultural setting, it was shown that higher exposures to mixtures of organophosphorus and pyrethroid insecticides resulted in lower sperm concentrations [56]. Pyrethroid insecticides are known to enhance the toxic effects of organophosphorus insecticides and apparently also enhance male infertility.

23.7.3 *Mild Steel Welding Fumes*

The composition of mild steel is as follows:

Carbon	0.03–1.25%
Iron	80–90%
Manganese	0.2–16%
Phosphorus	Max. 0.05%
Sulfur	Max. 0.05%
Silicon	0–0.5%

Fumes from welding mild steel can reasonably be expected to include vapors and particulates of the earlier list as well as carbon monoxide, carbon dioxide, fluorides, oxides of nitrogen, and ozone [78]. Welders of mild steel, but not stainless steel, have been found to have reduced semen quality and decreased fecundity compared with non-welders [79]. Welders are exposed to complex chemical mixtures that act via an unknown mechanism. It is interesting to note that one might have expected stainless steel welders to have a more adverse reaction due to the presence of chromium, which is an endocrine-disrupting chemical, but this is not the case.

23.7.4 *Tobacco Smoke*

It has been shown that nonsmokers produce about 50% more sperm than smokers and that sperm concentrations are 37% higher in nonsmokers than in smokers [80, 81].

Cigarette smoking is also a strong risk factor for erectile dysfunction (ED). In one study of the effect of smoking on ED it was shown that 1 year after ceasing smoking, 25% of those suffering from ED noted improved status, while 6.7% of those who continued to smoke for another year noted a decline in ED [82]. As was noted earlier smoking also impacts female fertility (as well as a host of other health issues).

23.7.5 *PCB and Phthalate Interaction*

PCBs and phthalates are endocrine-disrupting chemicals that adversely impact male fertility, especially sperm motility. In a sperm motility study, exposure to a mixture of PCB-153 and monobenzyl phthalate or monobutyl phthalate produced greater than expected negative impacts. The authors of the study hypothesized that the mechanism is through interactions between PCB metabolites and enzymes responsible for phthalate metabolism [83]. PCBs accumulate in body adipose tissue and metabolize slowly. Phthalates metabolize rapidly and are not known to accumulate in body tissues. Accordingly, it is more than likely that exposures to phthalates long after exposures to PCBs can produce enhanced negative sperm motility effects in men and dramatically reduce their fertility.

23.7.6 *Diesel Exhausts*

Diesel exhaust particle extracts were found to exert an antiandrogenic effect on human prostate carcinoma PCR/AR cells in vitro. A similar effect was observed

when equimolar mixtures of 10 PAHs, each having four or more rings (structures found in PAHs) at concentrations equivalent to those in the diesel exhaust particle extract [84]. These experiments demonstrate the antiandrogenic effect of high-molecular-weight PAHs and strongly suggest a role for diesel exhaust, a common air pollutant, particularly in urban environments, in male infertility.

23.7.7 Acrylates

Several years ago, while visiting a plastics and adhesive complex in the Far East, a worker confided in me that male colleagues of his working with acrylics were less fecund than those in the complex who did not work with acrylics and that when they did succeed in impregnating their wives, 80% of the children born were female. Acrylic polymers are not known to be antiandrogenic, but some of their plasticizers (such as bisphenol A and bisphenol A dimethacrylate) are xenoestrogens [85]. A check of the literature then and now does not reveal any reference to male infertility in acrylic workers. It is also unknown what other chemicals the affected workers may have been exposed to. The effect anecdotally reported to me remains a mystery. It should be noted, however, that paternal exposures to some chemicals are known to reduce the male:female ratios in offspring. For example, it has been shown that paternal exposure to dibromochloropropane during its production reduced the number of male offspring from 52.9%, before exposure to dibromochloropropane, to 35.2%, after exposure to this chemical [86].

23.8 Testicular Dysgenesis Syndrome

The recently proposed testicular dysgenesis syndrome (TDS) hypothesizes that four maladies, hypospadias, cryptorchidism, impaired spermatogenesis, and testicular cancer, are all manifestations of disturbed prenatal testicular development [87, 88]. Though this has not yet been demonstrated, TDS is believed to be connected to genetic and environmental factors. All four conditions noted have been independently related to endocrine-disrupting chemicals, and hence the association in TDS, which the authors of the most recent paper on the subject may be clinically manifest by a reduced sperm concentration [88].

23.9 Summary

Human infertility can result from the action of xenobiotic chemicals on the female reproductive system, the male reproductive system, attack on the fetus, and the induction of effects in utero that are manifested during adulthood, giving rise to a programmed infertility. SAB can ensue when pregnant women are exposed to toxic chemicals such as those in DBPs produced by the chlorination of drinking water.

Infertility in both women and men has increased dramatically during the latter half of the twentieth century, a time that saw a dramatic increase in the use of pesticides, plasticizers, and other endocrine-disrupting synthetic chemicals. Just recently it was found that bisphenol A, an endocrine disruptor that decreases fertility and fecundity, coats most cash register receipts in the United States, making human contact inevitable for most people [89–91].

Many single chemicals have been identified as endocrine disruptors, but little is known about the endocrine-disrupting effects of chemical mixtures. What little is known suggests that the effects of mixtures are greater than anticipated from the known toxicology of the mixture components. Infertility is increased by one of the most common mixtures to which humans are exposed, tobacco smoke.

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24 Teratogens

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24.1 Introduction

Teratogenic effects are those that cause malformations in the developing fetus and children. They can be genetically dictated, by environmental effects or multi-factorial (combinations of the two). Environmentally induced teratogenicity can be due to single chemical agents or mixtures of chemicals. Developmental toxins are those substances that can produce teratogenic effects during fetal and childhood development. Such effects include structural abnormalities, functional abnormalities, early birth, low birth weight, growth retardation, or death [1].

Most major structural malformations in the human fetus that are triggered by xenobiotics are initiated during the embryonic period of development, which ranges from third to eighth week of gestation. Birth defects, however, are not limited to exposures during this 5-week period. Teratogenic effects ensue when exposures occur during critical developmental events, key developmental steps that are completed by a particular developmental stage. Examples of critical developmental events include neural tube closing and separation of the heart into separate chambers. The urogenital system is an example of a late-developing system in the human embryo (occurring after 5–8 weeks of gestation). Though most teratogenic effects are believed to occur in the first trimester

of pregnancy, it is well established that developmental toxicity extends from conception through adolescence [2]. Fetuses and young children (those under 1 year of age) develop more rapidly than at any other time of life. This rapid development makes them particularly vulnerable to the actions of teratogenic chemicals. Air pollutants, for example, can lead to different degrees of exposure and hence to greater respiratory injuries in young children than in adults because children inhale greater quantities of air per unit surface area than adults [3]. There are also significant differences in pharmacokinetics between children and adults and even between children of different ages, with children metabolizing xenobiotics at rates that are significantly greater than the rates for adults [4].

Specific teratogens do not affect all individuals. For example, fewer than 20% of all infants exposed to thalidomide were adversely affected. It is commonly believed that some individuals have a genetic predisposition to impact by certain teratogens [2].

Teratogens are dose sensitive. Embryotoxicity is believed to be dependent upon multicellular injury and that there is a threshold dose below which there is no risk. The following example illustrates this point. Thalidomide provides an example. Human embryos are affected when a dose of 50 mg is taken by a pregnant woman during the susceptible period. A dose of 0.5 mg administered in the same critical period results in no observable effect [2].

Five specific mechanisms have been identified as those that disturb proper development. These include interaction with hormone receptors, covalent bonding to DNA, degradation of cell membranes or proteins, enzyme inhibition, and protein modification by interference with sulfhydryl groups [2]. It is important to note that teratogens with widely differing functional groups and reactivities can produce identical developmental effects. It is also noteworthy that mixtures of teratogens can simultaneously disturb more than one developmental mechanism and induce effects not expected from the actions of the mixture components.

Low birth weight, premature birth, behavioral and learning disorders, infertility, and structural birth defects are teratogenic effects with environmental triggers. Behavioral and learning disorders were discussed in Chapters 19–21 and infertility was addressed in Chapter 23. These will be covered only briefly in this chapter. This chapter will describe and reference the known effects of single chemical teratogens, but its emphasis will be on the teratogenic effects of chemical mixtures.

24.2 Single Chemical Teratogens

Numerous single chemicals have been identified as known or suspected developmental toxins [1, 5, 6]. Some of these chemicals, including pesticides, heavy metals, pharmaceuticals, and industrial chemicals, are listed in Table 24.1.

24.3 Paternally Transmitted Teratogenic Effects

Teratogenic effects can result from paternal as well as maternal exposures to toxic chemicals [7, 8]. Table 24.2 lists paternal occupations that have been associated with birth defects in offspring [8].

Table 24.1 Known or Suspected Developmental Toxins

1,2-Dibromoethane	Fluorouracil
2,4-Dinitrotoluene	Halothane
2,6-Dinitrotoluene	Heptachlor
2-Ethoxyethanol	Hexachlorobenzene
2-ME	Hydramethylnon
Arsenic	Linuron
Benomyl	Lithium carbonate
Benzene	Metham sodium
Bromomethane	Methanol
Bromo-oxylin	Methylmercury
Bromo-oxylin octanoate	Myclobutanil
Cadmium	Nabam
Carbon disulfide	Nicotine
Chlorosulfuron	Nitrapyrin
Cyanazine	PCBs
Cycloate	Phenol
Cyclohexanol	Phenytoin
DDT	Potassium dimethyldithiocarbamate
Disinfection by-products	Propargite
THMs	Sodium dimethyldithiocarbamate
HAAs	Tetracycline hydrochloride
Haloketones	Tetraethyl lead
HANs	Thalidomide
Dinitrobenzene (<i>ortho</i> , <i>meta</i> , and <i>para</i>)	Thiophanate-methyl
Dinitrobutyl phenol	Toluene
Dinocap	Triadimefon
Disodium cyanodithioimidocarbonate	TCE
Endrin	Triethylene glycol
Epichlorohydrin	Urethane
Ethanol	Vinclozolin
Ethyl dipropylthiocarbamate	Xylene
Ethylene glycol monomethylether	
Ethylene oxide	
Ethylene thiourea	

Source: Refs. [1, 3].

All these occupations have exposures to chemical mixtures associated with them. For most, the specific causative agents are unknown. Examples of paternal exposures leading to teratogenic effects will be given in Section 24.5.

24.4 Transgenerational Teratogenic Effects

It has been recently reported that paternal exposures to teratogenic effects can be transgenerationally transmitted. The following example illustrates this effect.

Table 24.2 Paternal Occupations Associated with Birth Defects in Offspring

Anesthetic gas use or proximity to its use
Automobile manufacturer
Carpenter
Electrical worker
Electronic equipment operator
Farm worker or manager
Firefighter
Food processor
Forestry and logging worker
Janitor
Jewelry maker
Material-moving equipment operator
Mechanic
Metal worker
Painter
Paint stripper
Plywood mill worker
Police officer
Printer
Sawmill worker
Welder

Source: Ref. [8].

Embryonic exposure to vinclozolin, an antiandrogenic endocrine disruptor, has been shown to promote prostate disease, kidney disease, immune-system abnormalities, testicular abnormalities, breast and other tumor development, and a number of blood abnormalities in the F1–F4 generations of laboratory animals [9, 10]. The effects observed were noted in the adults of the four ensuing generations that followed the exposure.

24.5 Teratogenic Mixtures

It has long been known that certain maternal occupational chemical exposures during pregnancy are associated with increased risks of congenital malformations in their offspring. In many instances, single chemicals have been identified as the causative agents. In other studies, the effects noted can only be attributed to unexpected impacts of chemical mixtures. The following studies are illustrative of the unexpected mixture effects.

24.5.1 Organic Solvents

Some single organic solvents, e.g., toluene, xylene, and ethanol, are known teratogens. Regrettably, many of the studies in the literature have lumped all organic solvent

Table 24.3 Organic Solvents Reported to Produce Teratogenic Effects [14] and Their K_{ow} Values

Chemical	K_{ow}	Known Teratogen	Known Endocrine Disruptor
Toluene	2.73	Yes	No
Xylene	3.15	Yes	No
Ethanol	-0.31	Yes	Yes
Methanol	-0.77	Yes	No
Isopropanol	0.05	No	No
Benzyl alcohol	1.10	No	No
<i>tert</i> -Butanol	0.35	No	No
Acetone	-0.24	No	No
Methylethyl ketone	0.29	No	No
Ethyl acetate	0.73	No	No
Hexane	3.90	No	No
Mineral spirits	4.10-6.5	No	Yes
Methylene chloride	1.25	No	No
1,1,1-Trichloroethane	2.49	No	No
TCE	3.40	Yes	Yes
Phenol	1.46	Yes	No
Propylene glycol	-0.92	No	No
Ethylene glycol	0.10	No	No
monomethylether acetate			
Triethylene glycol	-1.75	Yes	No

exposures together and have failed to identify the specific compounds or their exposure levels. It is accordingly difficult to draw meaningful conclusions about the teratogenic effects of both single compounds and mixtures. Several studies have drawn teratogenic conclusions, yet failed to identify specific compounds. Two investigations have shown that pregnant mothers who are exposed to unspecified organic solvents at work are more likely than those who are not so exposed to bear children with oral cleft and other congenital malformations [11, 12]. Another study found CNS defects in the offspring of women exposed to unspecified organic solvents during pregnancy [13].

One study that overcomes some of the shortcomings of those just cited reported adverse neurodevelopment outcomes following maternal exposures to 19 organic solvents and mixtures of these [14]. In this study, the women were occupationally exposed to the chemicals listed in Table 24.3. Also included in this table are the K_{ow} values and whether or not the specific chemical is a known teratogen or a known endocrine disruptor [5]. It is interesting to note that only three of the chemicals in the study, ethanol, TCE, and mineral spirits (a mixture of hydrocarbon solvents), are endocrine disruptors. This shows that teratogenic effects can be induced by chemicals and mixtures that are independent of the endocrine system.

The authors of this study acknowledged that associating specific chemicals with teratological effects is difficult since many of the exposures reported were to mixtures

of chemicals used simultaneously. From the occupations of the women included in the study, however, it is possible to approximate, if not accurately identify, the chemicals of exposure. Their occupations included laboratory technician, painter, science teacher, embalmer, hair stylist, chemical technologist, industrial laundry worker, conservator, carpenter, and salon receptionist. It is safe to say that employment in the areas just noted would almost always expose an individual to mixtures of lipophilic and hydrophilic chemicals. The levels of exposures to the individual chemicals were unavailable and not reported. However, since the study was carried out in Canada, a country with strict toxic exposure regulations, and reported in 2004, a time when permitted exposure levels for toxic chemicals were low, it is safe to say that levels of exposure in these industrial settings were such that allowable levels were generally not exceeded and that the effects reported must be attributed to mixtures (which produce adverse effects at lower concentrations than single chemicals) and not to single chemicals.

Paternal occupational exposure to organic solvents can also produce teratogenic effects. Painters, automobile-body-shop workers, printers, and fiberglass workers have all been shown to father children with low birth weight and congenital malformations [15, 16]. Workers in these occupations are continually exposed to mixtures of lipophiles (aliphatic and aromatic hydrocarbons) and hydrophiles (alcohols, ketones, and esters) while working. Many of the paints, adhesives, inks, and other materials used in these occupations have no known teratogens or have very low concentrations of teratogens, yet teratogenic effects are transmitted to the offspring of the men who work with these materials. It is unknown whether the teratogenic effects attributed to paternal exposures to organic solvents are due to injuries to sperm caused by these compounds and/or mixtures of these, or to deposition from seminal fluid in the mother's reproductive tract after impregnation [8]. Though it is generally acknowledged that paternal exposures can lead to teratogenic effects in their offspring, it is also possible that workers can "bring home" the teratogens on their clothing and equipment, leading to maternal exposure during pregnancy.

24.5.2 Wood Preservative Chemicals

Paternal exposures to dioxin-contaminated chlorophenols in the sawmill industry have been associated with congenital abnormalities of the eye, anencephaly or spina bifida, and congenital abnormalities of the genital organs of their offspring [17]. All the chlorophenols (from the monosubstituted to the pentasubstituted) are teratogenic [18]. The chlorinated dioxins are by-products of the chlorophenols and are also teratogenic [19]. One of these, TCDD, is a potent teratogen [20]. It is unknown what roles were played by the chlorinated phenols and the chlorinated dioxins or their mixtures in the adverse reproductive effects reported following paternal exposures to dioxin-contaminated chlorophenols in this sawmill-industry study [17].

24.5.3 Pesticides

Exposures to pesticides by pregnant women are well known to result in offspring with birth defects. The following examples are illustrative.

In a case report, a mother who applied DEET daily during her entire pregnancy gave birth to a child with craniofacial dysmorphism, mental retardation, and sensorimotor impairment [21].

Elevated risks of neural tube defects and other deformities were associated with maternal residence in proximity to agricultural pesticide applications in a California study. The risks were associated with amide, benzimidazole, methyl carbamate, or organophosphorus pesticide use. The risks were found to be greater when increasing numbers of pesticides were applied [22].

In a study in rural South Africa, a case-control study was conducted to investigate the association between pesticide exposure and the occurrence of birth defects. It was found that women who were exposed to pesticides in gardens and fields were 7 times more likely to give birth to babies with birth defects than women not so exposed. Deformed babies were also almost twice as likely to be born when their mothers dipped livestock in pesticides to prevent ticks and 6.5 times more likely to be born when their mothers fetched water with plastic containers that had previously held pesticides than cohort mothers who did not dip livestock or use pesticide-contaminated water containers [23].

A study in Washington state found that maternal exposure to agricultural chemicals (fertilizers and pesticides) produced an elevated risk of limb defects [24].

In one case study, it was shown that paternal exposure to pyridil herbicides (paraquat and diquat) was associated with congenital malformations in their offspring [25]. This study also found an association for congenital malformation from exposure to aliphatic hydrocarbons and inorganic compounds.

The results of the last study point out the difficulties in associating specific pesticide exposures to end results. As discussed in Chapter 14, pesticides are almost always applied admixed with solvents, surfactants, and other chemicals that aid in their solution, distribution, and adsorption. More often than not, mixtures of different pesticides are applied to achieve multiple effects. Such pesticide mixtures contain multiple lipophiles and hydrophiles, and the mixtures produce effects that are greater than those anticipated from the individual components. Accordingly, it should not be surprising that the teratogenic effects of pesticide mixtures should exceed those of the single species and produce enhanced detrimental outcomes in offspring.

24.5.4 Chemical–Radiation Mixture

Hyperthermia induced by an elevation in ambient temperature following RF radiation is known to be associated with fetal developmental effects. 2-ME is a known teratogen. In a study on laboratory animals, it was demonstrated that combined exposure to RF and 2-ME enhanced the adverse effects produced by either agent alone. It was also noted that teratogenic effects of 2-ME were observed at levels below those found for the solvent alone, when it was co-administered with RF [26].

24.5.5 Ethanol Mixtures

Thousands of studies have addressed the teratogenic effects associated with drinking ethanol during pregnancy. There are several mechanisms for the teratogenicity of

ethanol. It can kill brain cells, interfere with the transport of glucose and amino acids or impair placental–fetal blood flow, and interfere with hormonal and chemical regulatory systems in the brain that control the maturation and migration of nerve cells [2]. Consumption of too much ethanol by the mother during pregnancy can result in fetal alcohol syndrome (FAS), a pattern of mental and physical defects in offspring. FAS symptoms include [27]:

- Mental retardation
- Structural birth defects
- Abnormal facial features
- Growth problems
- CNS problems
- Difficulty learning
- Memory problems
- Vision problems
- Hearing problems
- Behavioral problems.

Mixtures of ethanol with other toxic chemicals produce unanticipated effects with greater teratogenic effects than ethanol or its mixture partners alone. The following study illustrates this phenomenon.

2-Ethoxyethanol is teratogenic to animals and humans [28, 29]. Concomitant exposure to a mixture of 2-ethoxyethanol and ethanol in the later stages of gestation potentiated the behavioral and neurotoxic effects of 2-ethoxyethanol alone in laboratory animals [30]. The authors of the study recommended that physicians advise pregnant women working with glycol ethers that consumption of ethanol during pregnancy could be particularly dangerous for them.

24.5.6 Air Pollution

Maternal exposure to air pollution during pregnancy, particularly during the first and third trimesters, is associated with preterm delivery and low birth weight. Several studies have addressed this topic and an analysis of these shows that elevated levels of sulfur dioxide, nitrogen dioxide, carbon monoxide, hydrocarbons, particulates, and ozone are all suspected as culpable [31–35]. Though a number of studies tried to tie the teratogenic effects to single pollutants, this could not be effectively done, as increases in one parameter (e.g., nitrogen dioxide) are almost always associated with increases in other values (e.g., ozone, carbon monoxide). As was discussed in Chapter 7, polluted air almost invariably contains a mixture of numerous lipophilic and hydrophilic chemicals that combine to cause often unanticipated toxic outcomes. Taken together, however, the studies cited produce powerful evidence that polluted air is teratogenic.

Polluted air causes postnatal developmental problems as well as prenatal ones. Studies in California have demonstrated that exposure to polluted air impairs lung development and lung function in children and young adults [36–38].

24.5.7 Paint

A study in the Netherlands reported congenital malformations in the offspring of male painters with occupational exposure to organic solvents [16]. Specific teratogens were not identified, but as has been previously discussed in Sections 12.5 and 13.5, both waterborne paints and oil-based paints contain mixtures of lipophilic and hydrophilic species. Exposures to both types of paints have been associated with low-level unexpected effects. Accordingly, the teratogenic results reported in the Dutch study are not surprising.

24.5.8 Hazardous Waste Site Proximity

Hazardous waste sites release mixtures of solvents into the air, and heavy metals, pesticides, and other organic compounds into surface and groundwaters. Several studies in different geographic settings have tied maternal residential proximity to increased teratogenic risks. These studies include the following.

A study in New York State found increased risk for congenital malformations in children whose mothers lived near hazardous waste sites during pregnancy [39]. A second New York study found elevated risks for CNS defects to be associated with residential proximity to hazardous waste sites that emit organic solvents or metals [40].

A California study found elevated levels of neural tube and heart defects in offspring to be associated with maternal residence within one mile of hazardous waste sites in the National Priority List of contaminated sites [41].

A study in Europe found a fairly consistent increase in risk for neural tube defects, malformations of the cardiac septa, and anomalies of great arteries and veins in offspring, the closer their mothers lived to hazardous waste landfill sites [42].

A Texas study found significant additional risk for congenital heart disease in children whose mothers lived close to hazardous waste sites than in children whose mothers did not live near toxic waste sites [43].

In Alaska, low birth weight and intrauterine growth retardation in babies were associated with maternal residency in villages that had open dumpsites containing hazardous materials in them [44].

Even though the exact nature of the injuries to the children involved varied from site to site, these studies, and others like it, taken together make a compelling case for the teratogenic hazards posed by emissions and leachates from hazardous waste sites. All such sites release complex mixtures of toxic chemicals with varying compositions. The particular composition from a given site no doubt influences which teratogenic injuries will be sustained by those whose mothers are exposed.

Four antiandrogens, di(2-ethylhexyl) phthalate (a widely used plasticizer in PVC and other plastics), vinclozolin and prochloraz (fungicides present in food), and finasteride (a pharmaceutical widely prescribed for benign enlarged prostate treatment) were tested on male laboratory rats. These four materials were chosen because they act via different mechanisms. When administered together, they acted synergistically in inducing malformations of external sex organs [45].

24.5.9 Tobacco Smoke

It is well known that smoking cigarettes during pregnancy is injurious to the developing fetus. The risks a smoking mother exposes her child to include reduced birth weight and deformities of the skull, extremities, and kidneys, enhanced susceptibility to respiratory diseases, reduced formation of new blood vessels, neurological damage, immune-system changes, and injuries to other organs [46–48]. These injuries have also been associated with maternal prenatal exposure to secondhand or passive smoking as well [47]. Though nicotine has been shown to be a neurological teratogen [49], and carbon monoxide poisoning has been associated with some deformities [46], the specific teratogens responsible for other effects remain unknown. A recent study has shown that prenatal exposure to cigarette smoke reduces the number of germ and somatic cells in embryonic male gonads [50]. Given the large number of toxic compounds and their multiple functional groups in tobacco smoke, much remains to be learned. The effects of mixtures of compounds present in tobacco smoke and their possible teratogenic effects require further research.

24.6 Summary

Endocrine-disrupting and non-endocrine-disrupting chemicals and mixtures of chemicals have been shown to be teratogenic. Environmental and on-the-job exposures can result in the adsorption of teratogenic chemicals that may have adverse effects on the developing fetus. Teratogenic effects can be transmitted to the human fetus by maternal exposure, paternal exposure, and even transgenerationally. The mechanisms for the actions of teratogenic mixtures remain largely unknown.

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25 Immune System

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25.1 Introduction

Tissue injury in the body can be caused by microbial infection, trauma, heat, radiation, or toxic chemical absorption. Whenever this occurs, the immune system immediately responds to the insult. A malfunctioning immune system can result in more severe injury or death.

Chemicals that attack the immune system render the body less capable of responding in times of need. Such chemicals are defined as immunotoxins, and immunotoxicology is the study of adverse health effects that result from the interactions of xenobiotics and the immune system [1]. Numerous individual chemicals, including benzene, PCBs, and dioxins, suppress immune system function in humans and lead to increased incidences and intensities of infectious diseases and cancer.

Immunotoxic effects can be manifested in three different ways. First, immunosuppression occurs when one or more of the immune system components is affected, resulting in a reduction in immune system function. Immunosuppression is manifested by decreased resistance to viral, bacterial, fungal, and other infectious agents and by increased susceptibility to cancer [2, 3].

Immunosuppression is not the only mechanism by which immunotoxins affect humans. Some chemicals, including anhydrides and isocyanates, are immunostimulants (also referred to as immunoenhancers), or allergens, compounds that stimulate specific immune responses and induce hypersensitivity (allergic reaction) in susceptible individuals.

Xenobiotics can also cause autoimmune diseases, conditions where healthy body tissue is attacked by an impacted immune system which does not discriminate between self antigens and foreign antigens.

The major components of the immune system are:

- Antibodies
- Bone marrow
- Complement system
- Lymph system
- Spleen
- Thymus
- White blood cells.

The complexity of the immune system renders it readily attacked by many chemicals. Such attack may result, for example, in organ damage in the thymus, bone damage and lymph nodes, as well as in cellular pathology in immunocompetent cells [4]. More than 350 different compounds have been identified as immunotoxins [5, 6]. Table 25.1 contains a representative list of these. This list includes heavy metals,

Table 25.1 Representative List of Immunotoxic Chemicals

Acrylic acid	Hydrazine
Arsenic	Hydroquinone
Benzene	Lead
Benzo[a]pyrene	Mercury
Beryllium	2-ME
Carbon tetrachloride	Methyl isocyanate
Chromium	Methylene chloride
Cobalt	Nitrogen dioxide
Cyclohexanone	PCBs
DDT	Phenyl hydrazine
1,2-Dichloroethane	Phthalic anhydride
<i>trans</i> -1,2-Dichloroethylene	Sodium dichromate
Dieldrin	TCDD
Diethyl phthalate	Tetrachloroethylene
Diethylamine	Toluene
7,12-Dimethylbenz[a]anthracene	Toluene diisocyanates
1,4-Dioxane	Trichloroethylene
Endosulfan	Triethanolamine
Epichlorohydrin	Trimellitic anhydride
Epoxy resins	Tungsten carbide
Ethyl acrylate	Turpentine
Ethylene oxide	Xylenes
Ethylene diamine	Zirem
Formaldehyde	

chlorinated and organophosphorus pesticides, aromatic hydrocarbons, PAHs, organic solvents, and many widely used chemicals. Many lipophilic and hydrophilic chemicals are immunotoxins and the immunotoxicity of these compounds is manifested via multiple mechanisms.

25.2 Immunosuppressants

A wide variety of structurally and functionally unrelated chemicals have been shown to be immunosuppressant. These include pesticides, PCBs, TCDD, polycyclic aromatic hydrocarbons, ethanol, and heavy metals [2, 5, 7–12]. The disruption of normal immune system function can be attributed to the compounds themselves or to their metabolites and can proceed by many different mechanisms [4, 13–15]. EMR, though not a chemical, has also been associated with immunosuppression, via as yet undefined mechanisms [16].

Exposure to xenobiotics reduces the effectiveness of childhood immunizations. In a study carried out on the Faroe Islands in the North Atlantic Ocean, it was found that the higher the level of PCB exposure, the lower the level of antibody protection in children against diphtheria and tetanus following routine immunization [17].

Immunosuppressant exposure also impacts the development of the immune system. Several studies have shown this effect [12, 13, 18] including one which examined TCDD, described in the study as “a notorious immunotoxicant” [12]. Other chemicals that cause developmental immunotoxicity include PCBs, polycyclic aromatic hydrocarbons, chlordane, DDT, HCB, methylmercury, lead, and cadmium [13].

25.3 Immunostimulants

Immunostimulants are substances that induce changes in the immune system such that further exposure to these and other chemicals leads to sensitization, i.e., recognition by the body and producing hypersensitivity, allergic responses that are greater and occur in response to lower doses than are observed in non-sensitized individuals. Inhalation of an allergen by a previously sensitized person can lead to rhinitis, conjunctivitis, and pulmonary symptoms, including bronchial constriction or obstruction as in asthma [19]. Examples of respiratory system sensitizers include trimellitic anhydride, toluene diisocyanate, methylhexahydrophthalic anhydride, platinum, nickel, chromium, cobalt, beryllium, epoxy resin catalysts, and ammonium persulfate [2, 5, 20]. Those with prior skin sensitization, as in ACD, react to contact allergens with swelling and/or rash when further exposed to dermal allergens [19]. 1-Chloro-2,4-dinitrobenzene, 2,4-dinitrofluorobenzene, and glycerol monothioglycolate (a reducing agent used in hair permanent waving solutions) are examples of dermal sensitizers [5, 21–24]. Some sensitizing chemicals can induce both contact dermatitis and asthma. Examples of these are toluene diisocyanate and trimellitic anhydride [21, 22].

Respiratory sensitization to chemicals may be acquired via dermal contact [25]. An example of this is the induction of airway sensitization in workers in a herbicide-producing plant that manufactured 3-amino-5-mercapto-1,2,4-triazole (AMT) by dermal contact. Experiments with mice confirmed the sensitization potential of AMT [26].

Dermal sensitization may follow prior respiratory sensitization. Hairdressers applying permanent waves containing glyceryl monothioglycolate as well as clients receiving such treatment have been shown to be more likely to develop ACD when they had previously become allergic to biological and chemical allergens [23].

25.4 Autoimmune Toxins

Exposures to xenobiotics have been associated with the onset of several autoimmune diseases. Lupus [systemic lupus erythematosus (SLE)], scleroderma (systemic sclerosis), rheumatoid arthritis, and other maladies have been strongly associated with exposures to single chemicals and mixtures of chemicals. The single chemicals include silica dust, VC, mercuric chloride, trichloroethylene, HCB, hydrazine, and tartrazine. Mixtures include epoxy resins, hair dyes, paint thinners and other (unspecified) organic solvent mixtures, industrial emissions, airborne particulate matter, and hazardous waste-site emissions [27–32].

The causal relationship between environmental exposure and autoimmune disease onset is seen from the data derived from studies of MZ twins. The concordance of autoimmune disease among such twins is only in the range of 25–40%, low enough to implicate environmental exposure, yet high enough to indicate genetic influences as well [32].

25.5 Immunotoxic Mixtures

The study of immunotoxic mixtures is complicated by the large number and diversity of chemical agents that are toxic to the immune system, multiple mechanisms by which the immune system is impacted, and exposures that are almost always to mixtures containing numerous immunotoxins.

Many POPs and other environmental contaminants have been associated with immunotoxic effects but, in most instances, it remains difficult to assign the effects to pure compounds. For example, immunotoxic effects of PCBs in free-ranging harbor seals have been associated with increasing blubber concentrations of PCBs [33], yet the waters inhabited by these animals are also contaminated with other POPs, including chlorinated pesticides and chlorinated PAHs. Indeed, the PCBs themselves are mixtures of different moieties with varying immunotoxic properties.

Several studies, however, have been able to demonstrate the immunotoxic effects of mixtures. Illustrative examples of these are as follows.

25.5.1 Benzene and Toluene

Benzene is a proven hematotoxic chemical, and toluene, too, is immunotoxic. Mixed together, however, in groundwater, toluene at low dosage does not protect against or contribute to benzene-induced immune functions in mice (involution of thymic mass and suppressions of both B-cell and T-cell mitogenesis). At high dose, however, toluene still did not demonstrate the immunotoxic effects attributed to benzene, but had an antagonistic effect on benzene immunotoxicity [34]. The authors of the study did not offer a mechanistic explanation for the observed phenomenon. It is thought, however, that by competing with benzene for metabolic action, the toluene may have suppressed the production of the benzene metabolites that are immunotoxic.

25.5.2 Pesticide and Fertilizer

Water contaminated with mixtures of the pesticides aldicarb ($K_{ow} = 1.13$) or atrazine ($K_{ow} = 2.61$) and nitrate ($K_{ow} = -4.39$) was administered to mice at concentrations simulating contaminated groundwater at levels found environmentally in midwestern United States farming communities. Though the pesticides alone are immunotoxic, nitrate is not. The mixtures of single pesticides with nitrate, however, reduced the ability to make antibodies against a foreign protein in laboratory animals [35]. No mechanistic explanation for this phenomenon was offered by the authors.

25.5.3 Propoxur and Heavy Metals

The mixture of the carbamate pesticide propoxur with either arsenic or mercury resulted in unanticipated changes in the spleens of laboratory animals orally exposed to the mixtures, when compared to the effects noted after treatment with propoxur, arsenic, or mercury alone [36].

25.5.4 Environmental Tobacco Smoke (ETS) Sensitization

Asthma is the most prevalent chronic disease affecting children worldwide and its prevalence has tripled in the last 30 years. Though a genetic predisposition is generally believed essential for asthma to ensue, environmental exposures to immunotoxins have been demonstrated to play a role in the induction of asthma. Two studies have shown that children exposed to ETS have increased incidences of asthma. Young children (aged 2 months to 5 years) who are exposed to ETS are more than twice as likely to be sensitized and to develop asthma than their cohorts who are not so exposed [37, 38].

25.5.5 Tobacco Smoke and Organic Solvents

Both tobacco smoke and aromatic organic solvents when acting separately diminish serum immunoglobulin levels in humans. Tobacco smoke as well as benzene and its homologs decrease serum IgA and IgG levels. Tobacco smokers also have reduced

IgM levels. The serum of tobacco smokers occupationally exposed to benzene and its homologs has been shown to have levels of all three immunoglobulins reduced to a greater extent than the reductions associated with either smoking or solvent exposure alone [39, 40]. Given the complexity of tobacco smoke as well as the presence of benzene in this smoke, it is at this time not possible to mechanistically account for the observed phenomena.

25.5.6 Tobacco Smoke and House Dust Mites

Human exposure to a combination of tobacco smoke and the house dust mite has been shown to result in allergic sensitization. It is believed that tobacco smoke impairs the barrier function of the airway epithelium, leading to increased access of allergens present in the house dust mite. In vitro studies with human bronchial epithelial cells have confirmed this hypothesis [41, 42]. In this instance it is believed that lipophiles in tobacco smoke serve to facilitate the permeation of the toxic allergens.

25.5.7 Air Pollution

A study of respiratory diseases induced by outdoor air pollutants has shown that allergic diseases are more prevalent in urban areas than in more rural places and are also more prevalent in industrialized countries than in developing nations. These increased prevalences have been associated with air pollutants, including oxides of nitrogen and sulfur, ozone, respirable particulates, and VOCs. The mixtures that are developed by these chemicals are complex and the mechanisms of their actions are still under investigation. It is known, however, that diesel-exhaust particles cause respiratory symptoms and are able to modulate the immune response in predisposed people by increasing immunoglobulin IgE synthesis. Evidence was also presented in this study demonstrating that air pollutants, like cigarette smoke, can interact with aeroallergens in the atmosphere and/or in human airways to potentiate their effects [43].

In a European study, it was shown that children living in two different industrialized areas, one containing chemical-manufacturing factories and the second the site of metal smelters, had greatly elevated prevalences of asthma and allergies than control children living in an area with clean air. The air in the chemical-manufacturing area was contaminated with the following lipophilic compounds:

- DDT
- Hexachlorocyclohexane
- PCBs
- Dioxins
- Furans.

The air in the smelting area was contaminated with arsenic, cadmium, chromium, lead, and nickel. It should be noted that both air polluted areas were further contaminated by oxides of sulfur and nitrogen produced by the burning of brown coal. Though much of the chemical composition of the polluted air was much different in

the two polluted areas, one primarily lipophilic and the other predominantly hydrophilic, the immunotoxic effects produced were similar. The children living in the smelting area were, however, more often sensitized to common aeroallergens [44, 45]. This suggests that multiple mechanisms may be responsible for the observed effects.

25.6 Multiple Chemical Sensitivity (MCS) and Chronic Fatigue Syndrome (CFS)

MCS and CFS are conditions with strong immunological factors. These will be examined in Chapter 26. The similarities and differences of MCS and CFS will be addressed at the end of Chapter 26.

25.7 Summary

Immunotoxic chemicals can interfere with the body's ability to ward off disease, can induce and exacerbate allergic responses, and contribute to autoimmune diseases. The complexity of the immune system and its interaction with other body systems make it particularly vulnerable to attack by xenobiotics. Studies that have been carried out, however, have demonstrated that a wide variety of chemicals are immunotoxic and that chemical mixtures such as those present in air polluted with the products of combustion, industrial emissions, and tobacco smoke are immunotoxic. Such polluted air can induce immunostimulative responses and bring on allergic reactions in previously sensitized individuals.

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26

Chemical Sensitivity: Multiple Chemical Sensitivity (MCS), Chronic Fatigue Syndrome (CFS), Fibromyalgia (FM), Gulf War Syndrome

Chapter Outline

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26.1 Introduction

Individuals with chemical sensitivity, also referred to as chemical intolerance, are those who react adversely to low levels of chemicals that are tolerated by the general population. These include multiple chemical sensitivity (MCS), chronic fatigue syndrome (CFS), fibromyalgia (FM), and Gulf War syndrome (GWS). Each is a clinically defined condition that can give rise to chemical sensitivity, but there is, however, considerable comorbidity between them. Each will be addressed individually, followed by a discussion of their similar responses to chemical stimuli.

26.2 Multiple Chemical Sensitivity (MCS)

MCS is a chronic condition in which multiple symptoms occur following exposure to chemicals at a single high level of exposure or multiple low levels of exposure (levels generally tolerated by healthy persons). The concept of sensitivity to multiple chemicals which was first described by Randolph in the 1940s [1, 2] may have existed for more than 100 years [3]. Studies in the United States, Canada, and Europe have shown that MCS severely affects about 3.5% of the population and moderately affects at least 12% of the population [4]. Diverse chemicals have been reported as causative agents for MCS. These include organic solvents, pesticides, hydrogen sulfide, mercury, and others [4].

Randolph characterized MCS as follows:

1. An acquired disorder following exposure to unusually high levels of an organic chemical.
2. Both psychiatric (depression, mania, hallucinations, and anxiety) and physical (arthritis, bronchospasm, and rhinitis) symptoms may be present.
3. Stimulatory syndromes (e.g., mania) may be triggered by acute exposures and be followed by withdrawal symptoms (e.g., headache, depression) hours to days after removal from an exposure.
4. *Adaptive phenomena*: Chemically sensitive individuals do not experience acute reactions while living in a chemical environment, but are chronically ill during this phase.
5. *Spreading phenomena*: As the illness progresses, the patient becomes susceptible to larger numbers of chemicals and has more serious symptoms.
6. *Avoidance*: The chemically sensitive person has resolution of his/her symptoms and remains well by avoiding the chemical environment.

Cullen, in 1987, was the first to use the term multiple chemical sensitivities. He described the syndrome as [5]:

... an applied disorder characterized by recurrent symptoms, referable to multiple organ systems, occurring in response to demonstrable exposure to many chemically unrelated compounds at doses far below those established in the general population to cause harmful effects. No single widely accepted test of physiologic function can be shown to correlate with symptoms.

Cullen's definition implies the following [6]:

1. MCS is acquired following a documentable environmental exposure that has caused clinically observable health effects.
2. The symptoms, which are referable to multiple organs, vary predictably in response to environmental stimuli.
3. Symptoms occur following exposures to measurable concentrations of chemicals, but these levels are below those known to harm healthy individuals.
4. Though symptoms are experienced in many organs, there is no evidence of organ damage.

Consensus criteria for the definition of MCS were established by researchers in the field in 1989 and edited in 1999 [7, 8]. These are:

1. *Symptoms are reproducible with [repeatable chemical] exposure.*
2. *The condition is chronic.*

3. *Low levels of exposure (lower than previously or commonly tolerated) result in manifestations of the syndrome (i.e., increased sensitivity).*
4. *The symptoms improve, or resolve completely, when triggering chemicals are removed.*
5. *Responses often occur to multiple chemically related substances.*
6. *Symptoms involve multiple-organ symptoms.*

Since 1999, science's understanding of MCS has expanded and the following, more precise working, definition of it was proposed in 2006 [9]:

1. *A medical condition manifested by recurrent symptomatic responses to chemical exposures at levels lower than previously or commonly tolerated.*
2. *Symptoms occur at levels of exposure below those generally known to cause adverse human effects.*
3. *The condition is chronic, persisting for at least three months.*
4. *Symptoms improve or resolve when exposure ceases.*
5. *Reactivity apparently spreads to include previously tolerated substances.*
6. *Symptoms occur with exposure to chemically diverse, unrelated substances.*
7. *For a given individual, similar symptoms generally occur with similar types of exposure to similar agents.*
8. *Symptoms vary markedly in terms of time to onset, recovery time, severity, frequency and duration.*
9. *Intolerance for previously tolerated alcohol and some pharmaceutical agents.*
10. *Symptoms are not limited to a single organ system.*
11. *Organ dysfunction that can be objectively verified is present, including but not limited to: cardiac, endocrine, immunological, neurocognitive neurological, and pulmonary; non-atopic rhinitis.*
12. *Neurobehavioral dysfunction is present, including diminished mental acuity and mood alterations (such as reactive depression, irritability, anxiety tension, confusion, fatigue and anger).*
13. *Difficulty with maintaining usual habits and activities of daily living and reduced quality of life, and ability to access hospital and medical services. Examples: ability to go to work or school; choice of personal care products, clothing, food and home location; ability to travel to other cities or drive a car; ability to be around others and enjoy social activities such as going to meetings, places of worship, restaurants; choice of hobbies or recreation; ability to perform home maintenance chores.*

Other names for MCS include [10, 11]:

Environmental hypersensitivity
Total immune disorder syndrome
Twentieth-century disease
Total allergy syndrome
Environmental illness
Sick building syndrome
Idiopathic environmental intolerance
Chemical AIDS
Environmentally induced disease
Cerebral allergy

Chemically induced immune dysregulation
Ecological illness
Food and chemical sensitivities.

In the United States, more than 45 million people have reported sensitivities to various chemicals. Of these, more than 3 million have been formally diagnosed with MCS. MCS affects diverse populations; people of all ages, both genders, economic status, and race [12]. Both indoor and outdoor exposures can trigger reactions in sensitive individuals. Perfumes, deodorants, cleaners, scented laundry and other cleaning products, pesticides, herbicides, organic solvents, chlorine, paints, adhesives, building materials, home furnishings and carpets, gasoline, petroleum products, artificial flavors and colors, preservatives, and some medications have been shown to trigger reactions [13].

Clinical ecology, a branch of medicine that believes that foods and environmental chemicals can be responsible for illnesses with multiple symptoms that lack objective physical markers, defines ecological illness as follows [14]:

Ecological illness is a polysymptomatic, multisystem chronic disorder manifested by adverse reactions to environmental excitants, as they are modified by individual susceptibility in terms of specific adaptations. The excitants are present in air, water, drugs, and our habitats.

William Rea is the leading practitioner of clinical ecology. His Environmental Health Center in Dallas, Texas, has diagnosed more than 20,000 patients with chemical sensitivities. Rea defines chemical sensitivity as follows [15, 16]:

Chemical sensitivity is defined as an adverse reaction to ambient doses of toxic chemicals in our air, food and water at levels which are generally accepted as sub-toxic. Manifestation of adverse reactions depends on

- (1) the tissue or organ involved;*
- (2) the chemical and pharmacologic nature of the toxin;*
- (3) the individual susceptibility of the exposed person (genetic makeup, nutritional state and total [toxic] load at the time of exposure);*
- (4) the length of time of the exposure;*
- (5) the amount and variety of other body stresses (total load) and synergism at the time of reaction;*
- (6) the derangement of metabolism that may occur from the initial insults.*

26.2.1 MCS Symptoms

Those with MCS experience a wide variety of cardiac, respiratory, endocrine, hepatic, immunological, nervous system, and musculoskeletal organ symptoms [6, 17, 18]. Table 26.1 contains a partial list of symptoms associated with MCS.

As can be seen from Table 26.1 a very large number of symptoms have been associated with MCS. The symptoms most commonly encountered are those of the CNS, respiratory and mucosal irritation, or gastrointestinal ones, and to a lesser extent musculoskeletal ones [6, 17].

Table 26.1 Partial List of Symptoms Associated with MCS

Abdominal pressure, pain, cramps	Joint pain
Anaphylactic shock	Lethargy
Anger	Lightheadedness
Anxiety	Low energy
Attention deficit	Memory problems
Blurring of vision	Muscle pain, spasm
Breathing difficulty	Muscle twitching
Chest pain	Nausea
Cognitive dysfunction	Nerve pain
Confusion	Numbness, tingling
Contact dermatitis	Overactive bladder
Coordination difficulties	Panic
Coughing	Paralysis
Diarrhea	Reduced tolerance to heat or cold
Dizziness	Restless leg syndrome
Dry eyes	Seizures
Dry mouth	Sinus discomfort
Fatigue	Skin irritation
Fever	Skin rash
Food intolerance	Sleep disturbances
Headache	Slurred speech
Hearing changes	Sneezing
Heart palpitations	Swollen glands
Heartburn	Tendonitis
Hives	Trembling
Immune system suppression	Unusual thirst
Inability to concentrate	Vertigo
Inability to focus vision	Vomiting
Indigestion	Weak voice, hoarseness
Itchy eyes or nose	Weakness

26.2.2 Causative MCS Chemicals

A large number of chemicals have been shown to precipitate MCS. The sources of these chemicals include industrial chemicals, off-gassing in tightly sealed buildings, polluted air and water in areas contaminated by industrial discharges and toxic waste site releases, and from use of consumer products, including pharmaceuticals, personal care products, paints, adhesives, pesticides, and other chemical products used around the home. Table 26.2 lists some of the individual compounds that have been associated with MCS [15–19].

Though many single chemicals have been implicated, most of those who are affected with MCS are sensitized by and react to chemical mixtures [6, 16, 20–22]. Some of the mixtures that trigger MCS arise from the sources listed in Table 26.3.

As described in earlier chapters in this book (Part II), virtually every one of the MCS-triggering sources listed in Table 26.3 contains mixtures of lipophilic and hydrophilic chemicals.

Table 26.2 Single Chemicals Associated with MCS

Aluminum	Glycine
Benzoyl peroxide	Mercury
Carbon tetrachloride	Phenol
Chlordane	Platinum
Chlorine	Toluene
Chlorpyrifos	TDI
DDT	TCE
Ethyl methacrylate	Xylene
Formaldehyde	

Table 26.3 Chemical Mixtures that Trigger MCS

Aerosol air fresheners	Household cleaners
Aerosol deodorants	Insect repellents
Aftershave lotions	Laundry detergents
Asphalt pavements	Marking pens
Carpet emissions	Nail polishes
Cosmetics	Nail polish removers
Deodorizers	Paint removers and strippers
Diesel exhausts	Perfumes and colognes
Diesel fuel fumes	Pesticides
Dry-cleaning fluid	Roofing tar
Floor cleaners	Shampoos
Furniture polishes	Solvent-based paints
Gasoline exhausts	Tobacco smoke
Gasoline fumes	Varnishes
Hairsprays and treatments	

26.2.3 MCS Mechanistic Considerations

MCS affects multiple, often unpredictable and seemingly unrelated, body sites. Different explanations have been proposed to explain this phenomenon. These are discussed here under the headings of the researchers who are their primary proponents: William J. Rea, Iris R. Bell, and Martin L. Pall.

William J. Rea

Rea instructs that several principles must be considered to demonstrate the influence of environmental chemicals on chemical sensitivity. These include total body load, adaptation, bipolarity, biochemical individuality, spreading, and switch phenomenon [15, 16].

Total Body Load

Total body load (burden) is the total pollutant load from whatever source that the patient carries. This can include organic chemicals, heavy metals, and other inorganics, as well as biological matter (bacteria, viruses, parasites, molds, and food).

Adaptation

Adaptation addresses the body's ability to increase body load without apparent symptoms, despite the fact that continued toxic exposures may continue to damage the immune and enzyme detoxification systems (xenobiotic metabolic processes). At some point, such continued accumulation results in end-organ failure.

Bipolarity

Following toxic exposure, the body develops a bipolar response of a stimulatory phase followed by a depressive phase, with the induction of immune and enzymatic detoxification systems. If the toxic insult is great enough, the induced immune and enzyme detoxification systems are depleted or depressed by overutilization and overstimulation. Bipolarity helps explain why symptoms may not be obviously related to exposures, but ensue following later exposures.

Biochemical Individuality

Biochemical individuality addresses the unique genetic susceptibility of the individual. A group of people can be exposed to the same pollutant. One may develop arthritis, sinusitis, cystitis, asthma, diarrhea, and one may remain unaffected.

Spreading

This phenomenon occurs when sensitization to one chemical leads to low-dose reactions to many other chemically unrelated substances.

Switch Phenomenon

Switching refers to the changing of one end-organ response to another end organ. For example, during a 24-h reaction the same toxic chemical exposure can start off as transient brain dysfunction and be followed by arthralgia, diarrhea, and then arrhythmia.

Iris R. Bell

Bell et al. have proposed a neural sensitization model to account for the observed hypersensitivity on some individuals to low-level chemical exposures in MCS [20, 23–25]. These researchers describe neural sensitization as the progressive host amplification of a response over time from repeated, intermittent exposure to a stimulus. They report that drugs, chemicals, endogenous mediators, and exogenous stressors can all initiate sensitization and exhibit cross-sensitization between different types of stimuli. Laboratory studies with animals have demonstrated sensitization to several toxic chemicals, including formaldehyde, toluene, and pesticides. Animal studies have also shown cross-sensitization with formaldehyde and cocaine. Human laboratory studies with chemically intolerant humans have shown heightened sensitization-specific chemical exposures as well as to nonspecific experimental challenges [23].

Bell et al. described an olfactory-limbic and neural sensitization mechanism for MCS. The following quotation from their 1977 paper describes the phenomenon [20]:

The olfactory-limbic and neural sensitization model proposes that individual differences in reactivity to environmental substances in MCS derive from neurobiologically based sensitization of the olfactory, limbic, mesolimbic and related pathways of the CNS. The nose is a direct pathway into the limbic system for both neural signals and for transport of many molecules. Among the sensory systems, only the olfactory system lacks a blood-brain barrier. The olfactory bulb, amygdala and hippocampus are interconnected parts of a phylogenetically older portion of the brain that is particularly vulnerable to sensitization processes. Repeated intermittent exposures to a given stimulus lead to progressively increased levels of responsivity over time in those structures. Sensitization then persists without reexposures for long periods of time.

In a following paper on sensitization in chemically intolerant individuals, Bell and her colleagues write:

'Stressor' refers to an environmental factor of any category (chemical, physical or psychological) that the individual experiences as significant and thus places demands for adaptation upon the organism as a whole. Sensitization is the progressive amplification of host responses to repeated, intermittent exposures to an initiating stimulus or stressor. Allostasis is 'the regulation of the internal milieu through dynamic change in a number of hormonal and physical variables in which there is anything but steady state.' The compensatory and anticipatory nervous system and neuroendocrine changes that produce short-term coping for the individual lead to 'allostatic load' and long-term costs from the development of chronic disease. Sensitization is one pathway into allostatic load. The manifestations of chronic disease for persons with chemical intolerance reflect individual differences in genetic and gender potential [primarily women] for dysfunction in different psychological subsystems interacting with the current environment.

Martin L. Pall

Pall has proposed that elevated nitric oxide/peroxynitrite levels are implicated in MCS. Peroxynitrite is formed by the reaction of nitric oxide with superoxide, which in turn results from the action of ROS (Section 4.9). Pall summarizes the evidence for the nitric oxide/peroxynitrite theory in the following 10 steps [26, 27]:

1. Several organic solvents thought to be able to induce MCS, formaldehyde, benzene, carbon tetrachloride, and certain organochlorine pesticides all induce increases in nitric oxide levels.
2. A sequence of action of organophosphate and carbamate insecticides is suggested whereby they may induce MCS by activating acetylcholinesterase and thus produce increases in nitric oxide.
3. Evidence for induction of inflammatory cytokines by organic solvents that induce the inducible nitric oxide synthase (iNOS). Elevated cytokines are an integral part of the proposed feedback mechanism of the elevated nitric oxide/peroxynitrite theory.
4. Neopterin, a marker of the induction of iNOS, is reported to be elevated in MCS.

5. *Increased oxidative stress has been reported in MCS; antioxidant therapy may produce improvements in symptoms, as expected if levels of oxidant peroxynitrite are elevated.*
6. *In a series of studies of a mouse model of MCS involving partial kindling and kindling, excessive NMDA activity and nitric oxide synthesis were shown to be required to produce the characteristic biological response.*
7. *The symptoms exacerbated on chemical exposure are similar to the chronic symptoms of CFS [chronic fatigue syndrome]; these may be explained by several known properties of nitric oxide, peroxynitrite and inflammatory cytokines, each of which have a role in the proposed mechanism.*
8. *These conditions (MCS, CFS ...) are often treated through intramuscular injections of vitamin B-12; B-12 in the form of hydroxocobalamin is a potent nitric oxide scavenger in vitro and in vivo.*
9. *..... Peroxynitrite is known to induce increased permeabilization of the blood–brain barrier; such increased permeabilization is reported in a rat model of MCS.*
10. *Five types of evidence implicate NMDA activity in MCS, an activity known to increase nitric oxide and peroxynitrite levels.*

The NMDA receptor is a receptor for glutamate, the most important excitatory neurotransmitter in the brain. Pall has further theorized that MCS is accompanied by excessive NMDA activity. He attributes this to four factors:

1. Nitric oxide stimulates the release of glutamate.
2. Peroxynitrite depletes ATP, causing NMDA receptors in depleted cells to be hypersensitive to stimulation.
3. Peroxynitrite increases permeability of the blood–brain barrier to organic compounds.
4. Nitric oxide inhibits cytochrome P450 metabolism of organic compounds, resulting in the presence of increased concentrations of organic compounds that may stimulate NMDA activity [26].

The mechanisms proposed by Rea, Bell, and Pall are not incompatible. Each addresses MCS from a different angle, and all three are valid. Rea attributes MCS to a weakened immune system and altered metabolism. Bell proposes that neurosensitization is the key to MCS induction, and Pall theorizes a molecular biological explanation. There are differences, however.

MCS sensitization and manifestation has been linked to both volatile and nonvolatile compounds, organic and inorganic. Neurosensitization resulting from inhalation does not explain sensitization from the ingestion of nonvolatile compounds such as those found in contaminated water and tainted foods nor does it account for the dermal absorption of xenobiotics known to cause sensitization. The neurosensitization and molecular biological approaches do not address switching of symptoms resulting from the same exposure to different organs of the body. The model proposed by Rea does not attempt to address the molecular biological approach as the Bell and Pall models do.

26.2.4 MCS Mixture Effect

The Pall and Bell theories are based upon observed responses to single chemicals. Rea's approach considers mixtures of contaminants as always present, but makes no attempt to ascribe effects to particular mixtures. The theme of this book is that

exposures to mixtures of lipophilic and hydrophilic toxic chemicals induce unanticipated effects, including low-level responses, greater than anticipated effects and attacks on unanticipated organs. Also, there are numerous examples of case studies where multiple organs are affected by low levels of the same mixtures. The following studies are illustrative of such multi-organ effects. The K_{ow} values, given in parentheses, demonstrate the lipophilicity or hydrophilicity of the chemicals involved.

1. More than half of approximately 200 employees working with composite plastic materials in one building of an aircraft manufacturing plant reported CNS, respiratory, heart, and gastrointestinal symptoms. Phenol (1.46), formaldehyde (0.35), styrene (2.95), methylene chloride (1.25), methanol (−0.77) as well as several lipophilic aliphatic and aromatic hydrocarbons were found in the air of the building. All exposures were at levels below PEL [28].
2. A “mystery illness” that affected 17 casino workers with respiratory and CNS symptoms following fumigation with a mixture consisting of propoxur (1.52), coumaphos (4.13), 1,1,1-trichloroethane (2.49), methylene chloride (1.25), xylene (3.15), and acetone (−0.24). Industrial hygiene evaluation showed only trace quantities of the chemicals noted [29].
3. A laboratory study on mice found that there was little or no observed effect when water containing nitrates (−4.39) alone, aldicarb (1.13) alone, or atrazine (2.61) alone at groundwater MCL levels was consumed. When consumed together, however, in drinking water at the MCLs for groundwater, the mixture altered immune, endocrine, and nervous system parameters [30].

It has been proposed by this writer that when toxic mixtures are composed of lipophiles and hydrophiles, the lipophilic species facilitate the absorption of the hydrophilic ones and/or metabolites and thereby induce increased toxic effects compared to those caused by the single chemicals [31, 32]. The complicating factor in addressing MCS and its mechanisms is that the toxic environmental mixtures that people in the real world are exposed to are multifaceted and constantly changing. Not only are the individual species changing, but the proportions of lipophiles and hydrophiles are also constantly in flux. For example, an individual may simultaneously eat food contaminated with variable levels of residual pesticides and other persistent organic pollutants, breathe air polluted with varying levels of diesel exhaust, ozone, and VOCs, and drink water containing ever-changing quantities of DBPs, heavy metals, and other contaminants. A large number and great variety of chemical products and environmental mixtures are known to trigger MCS (Table 26.3). Given this complexity and the large number of symptoms associated with MCS (Table 26.1), this is not surprising. This variability in exposure and symptoms invites multiple mechanistic explanations, such as those offered above.

26.3 Chronic Fatigue Syndrome (CFS)

CFS, also known as chronic fatigue and immune dysfunction syndrome (CFIDS) and myalgic encephalomyelitis, is a multisystem disorder with unknown etiology or pathophysiology. It is currently thought that CFS is a multifactorial condition in which an infective agent causes an aberrant immune response. It is characterized by extreme fatigue, immune system dysfunction, neurological and endocrine disorders, chronic pain, and numerous other symptoms. Many of those with CFS are extremely sensitive to chemical exposure [33–38].

CFS is diagnosed by its symptoms following the elimination of other possibilities. For a person to be diagnosed with CFS, she or he must meet the following two criteria [33, 38]:

Unexplained persistent or relapsing fatigue for at least six months duration that is

- [1] of new or definite onset,*
- [2] not the result of ongoing exertion,*
- [3] is not substantially alleviated by rest,*
- [4] and results in substantial reduction in previous levels of occupational, educational, social, or personal activities*

and

Four or more of the following eight symptoms, persistent or relapsing, for at least six months:

- [1] impairment of short-term memory or concentration;*
- [2] sore throat;*
- [3] tender cervical or axillary lymph nodes;*
- [4] muscle pain;*
- [5] multi-joint pain without joint swelling of redness;*
- [6] headaches of a new type, pattern or severity;*
- [7] unrefreshing sleep; and*
- [8] postexertional malaise lasting more than 24 hours.*

The onset of CFS is generally thought to be preceded by a viral infection and flu-like illness, but, despite numerous studies, no etiologic agent has been identified. A recent study identified DNA from a xenotropic murine leukemia virus-related virus (XMRV) in peripheral blood mononuclear cells in 67% of blood in patients with CFS, but only in 3.7% of the blood in healthy individuals [4]. It is not known at this time if this or other viruses play a causative role in the development of CFS.

In patients with CFS, the CNS, immunological, and endocrine systems are affected [39]. Symptoms may be exacerbated by infection, stress, and environmental agents, including organophosphate pesticides and other toxic chemicals [36]. As discussed later, many of those with CFS are extremely sensitive to chemical exposure, and claims that chemicals are causative agents for the onset of CFS have been made.

CFS, first discovered in Nevada in the 1980s [40], is prevalent worldwide, is more prevalent in women than in men, and occurs as isolated cases or in clusters [36, 40–48]. In a recent study carried out in Georgia (U.S.), the prevalence of CFS was estimated at 2.54% of people aged 18 to 59 years. The study found no significant differences in the prevalence of CFS between metropolitan, urban, or rural areas, nor between Caucasian and African-American residents of the state [48]. Though this number is believed to be fairly well representative of the prevalence rate reported in the industrialized world, the actual numbers of cases may be higher due to a lack of recognition and underreporting of CFS cases.

It has been hypothesized that the same elevated nitric oxide/peroxynitrite mechanism described for MCS (Section 26.2.3) [26] also applies to CFS [49–55]. In this

hypothesis, CFS symptoms are ascribed to nitric oxide, peroxynitrite, and related hypoxia as follows [50]:

Symptom	Cause
Fatigue, loss of energy	Peroxynitrite attack on mitochondrial function; hypoxia
Immune dysfunction	Elevated OS (peroxynitrite)
Cognitive dysfunction	Elevated nitric oxide in the CNS; CNS hypoxia
Pain	Nitric oxide stimulation of nociceptors
Intense fatigue after exercising	Superoxide generation by hypoxia

26.4 CFS and Chemical Exposure

Patients with CFS often react to chemical exposures in a similar manner to those with MCS. Though, as discussed earlier, the initial onset of CFS is widely believed to be preceded by a viral infection or flu-like illness, CFS cases have been reported following chronic and acute exposures to chemicals. These are:

1. Three clusters of CFS have been associated with poor indoor air quality. In the first, 9 of 10 teachers in Truckee, California, using a conference room that was contaminated with fumes from a spirit copy machine, cigarette smoke, and continually recycled air, developed clinical symptoms consistent with CFS. The second involved 23% of the 22 teachers in a school in Elk Grove, California, who worked in the same wing of the school, a poorly ventilated area with gasoline engine exhausts and volatile organic chemicals from an adjoining art room. In the third cluster, 10% of the 93 workers in an office building with no functioning windows in Washington, DC, were affected. Though 83% of the workers in the building described the air in it as stuffy, industrial hygiene evaluations of the building failed to identify any air quality abnormalities [56].
2. Researchers at the National Reference Center for CFS Study at the Department of Infectious Diseases of G. D'Annunzio University in Chieti, Italy, reported that five CFS individuals developed clinical features of CFS several months after their exposures, two to the food poison ciguatera and three to organic solvents [57].
3. CFS was reported in 10 farmers in the United Kingdom as a delayed reaction following chronic low-dose exposure to organophosphates, including malathion [58]. The onset of CFS symptoms in all except one was preceded by a flu-like illness. In the tenth, CFS was preceded by cholecystitis. Due to this, it is not clear that the pesticide exposures alone were the CFS causative agents in this study.
4. Organophosphate pesticides were identified as causative CFS agents in a questionnaire study of sheep farmers in the United Kingdom. These individuals regularly dip their sheep into these insecticides to control lice and other pests, resulting in large dermal exposures. In this study, a high prevalence of CFS was reported. Elevated chronic fatigue scores were associated with higher exposure levels and increased levels of symptoms in the affected farmers [59].
5. Pesticides were further implicated as causative agents for CFS in a Spanish study that reported on 26 people who developed CFS following their return to a workplace that had been fumigated [60].

With the exception of the Spanish study, all the reported CFS cases followed long-term, chronic exposures or disease onset long after exposure. In the British

study, infections immediately preceded the reported onset of CFS. These studies, while suggestive, do not establish a causal relationship between chemical exposure and CFS. CFS has immune, nervous, and endocrine system involvement. It should not be surprising, however, that chemicals that affect these body systems can contribute to, if not be a cause of, CFS. This subject will be pursued further in Section 26.8 below.

The most compelling evidence for the association between chemical exposure and CFS comes from the fact that many veterans of the Persian Gulf War in 1991 have been diagnosed with CFS following their exposures in the Persian Gulf. This subject will be explored in Section 26.6 later.

26.5 Fibromyalgia (FM)

FM is a widespread musculoskeletal pain and fatigue disorder. It affects about 5% of the population in the United States, mostly women, and is characterized by widespread pain, decreased pain tolerance, fatigue, difficulty sleeping, depression, and other psychological symptoms. Though the cause of FM remains unknown, many events are thought to trigger its onset. These include a viral or bacterial infection, the development of rheumatoid arthritis, lupus or hypothyroidism, or a traumatic event such as an automobile accident [61, 62]. A recently published study has found that FM female patients have a higher frequency of childhood ADHD compared with healthy women. The same study reports that FM and ADHD share some clinical features and that both disorders may have common etiopathological features [63].

Symptoms of FM include:

Pain	Chronic widespread pain described as burning, throbbing, shooting, or stabbing. Upper back, lower back, neck, shoulders, and other areas around joints are the painful areas.
Fatigue	Fatigue can be mild to profound, with some patients feeling drained all over and left incapable of accomplishing daily activities.
Sleep disorder	Most FM patients have an alpha-EEG sleep disorder, with deep-level sleep being constantly disrupted.
Irritable bowel syndrome	Approximately 40–70% of FM patients frequently have constipation, diarrhea, abdominal pain, abdominal gas, and nausea.
Chronic headaches	Recurrent migraine or tension-type headaches are prevalent in about half of those with FM.
Temporomandibular joint dysfunction syndrome	Tremendous face and head pain seen in about 25% of patients with FM.
MCS	Approximately 50% of FM patients have the symptoms associated with MCS.
Other symptoms	Other common symptoms of FM include chest pain, morning stiffness, cognitive or memory impairment, dizziness, impaired coordination, numbness and tingling sensations, irritable bladder, twitching, dry eyes, or mouth and skin sensitivities.

As can be seen from this list of symptoms, many are emblematic of MCS and CFS. This crossover of symptoms often complicates the diagnosis of FM. Mechanistically, OS and nitric oxide are believed to play a role in FM pathophysiology; however, it is not at this time clear whether the OS abnormalities found in FM are the cause or the effect [50, 64].

One study relating chemical exposure to FM has been published. In it, four FM patients diagnosed with FM are reported to have complete or nearly complete resolution of their symptoms within months of eliminating two excitotoxins, MSG or MSG plus aspartame, from their diets [65]. The authors point out that excitotoxins act as excitatory neurotransmitters that can lead to neurotoxicity when excessively consumed. No other similar studies have been found.

26.6 Gulf War Syndrome (GWS)

GWS is an illness with multiple symptoms that affects veterans of the Persian Gulf War in 1991. The symptoms reported include [66]:

- Chronic fatigue
- Loss of muscle control
- Muscle and joint pain
- Headache
- Dizziness
- Loss of balance
- Cognitive and memory problems
- Indigestion
- Skin disorders
- Dyspnea
- Indigestion
- Diarrhea.

The cause of GWS is unknown, but seems to be related to chemical exposures that soldiers were exposed to during their service in the war. These include:

- Smoke from oil well fires
- Diesel exhausts
- Combustion products from depleted uranium munitions
- Pesticides and insect repellants
- PB, administered to troops to protect against injury by nerve gas agents.

As discussed in Section 18.6, military personnel were administered PB and also exposed to DEET (an insect repellant) and permethrin (an insecticide), the combination of which produced unanticipated neurological symptoms [67]. When the exposures from diesel exhaust, oil-well fire smoke and spent munitions combustion products are added to these, the onset of other unexpected health effects is not surprising. It is to be noted that the chemical mixtures to which the military personnel were exposed included large numbers of lipophilic and hydrophilic species.

More than 100,000 of the 700,000 U.S. veterans, as well as similar numbers of veterans of other nationalities who participated in the Gulf War, have registered with

the Veterans Administration as having Gulf exposure-related illnesses [68–72]. Many of these individuals have symptoms that meet the criteria for MCS and CFS [73, 74]. Since other causative exposures have been seemingly ruled out, the large number of CFS patients found among Gulf veterans compels a strong argument for chemical mixture exposure being a cause of at least some cases of CFS.

26.7 Comorbidity of MCS, CFS, and FM

Patients with MCS, CFS, and FM report many of the same symptoms, including myalgia, fatigue, sleep disturbances, and impairment of their ability to perform daily activities. There is also considerable comorbidity of these syndromes in affected patients [75–78]. The following studies are illustrative:

1. Severe chemical intolerance is prevalent among 20–47% of patients with MCS, CFS, and/or FM [76].
2. In one study, 37% of CFS patients met the clinical criteria for FM and 33% met the criteria for MCS [79].
3. In a second study, 70% of patients with FM and 30% of those with MCS met the clinical criteria for CFS [80].
4. A third study reported that of patients with CFS, 40.6% met the clinical criteria for MCS and 15.6% for FM [77].
5. A fourth study found that of people who met the criteria for CFS, 43.9% had CFS alone, 23.7% met the criteria for CFS and MCS, 15.8% met the criteria for CFS and FM, and 16.7% met the criteria for CFS, MCS, and FM [78].

It has been proposed that the presence of comorbid illness among patients with MCS, CFS, and FM supports a single syndrome hypothesis, i.e., that all are variants of a single functional disorder [79]. This is supported by the nitric oxide/peroxynitrite hypothesis that has been previously discussed [26, 49–52] and by the shared symptoms in Gulf War veterans [73, 74]. It is argued here, however, that though these illnesses have overlapping symptoms, this hypothesis is yet to be definitively proven. Each of the illnesses has distinct differences from the others and at least one, MCS, demonstrates a resolution of symptoms when exposures to the causative chemicals are eliminated.

26.8 Chemical Sensitivity Triggers Hypothesis

MCS has been shown to be caused by chemical exposure and there is evidence and mechanistic support for chemicals being the causative agents for CFS and FM. It is proposed here that chemicals may, indeed, be causative agents for all chemical sensitivity syndromes for the following reasons:

1. Large numbers of Gulf War veterans who were exposed to complex chemical mixtures have been diagnosed with MCS and CFS [73, 74].
2. A number of CFS clusters have been identified with indoor chemical exposures [56] as well as with exposure to organic solvents and organophosphate pesticides [57–59].

3. Resolution of FM symptoms has been associated with the dietary removal of excitatory neurotransmitters [65].
4. All three conditions and their symptoms can be explained by a common nitric oxide/peroxynitrite mechanism [26, 49–53].
5. All three conditions are manifested by immune, neurologic, and endocrine factors [16, 38]. Numerous chemicals and chemical mixtures are known to affect the immune, CNS, and endocrine systems (Chapters 18, 22, and 25). Chemicals or chemical mixtures that are toxic to these three systems would be expected, at the very least, to exacerbate other causative effects, or to act alone as causative agents.
6. Hundreds of single chemicals have been identified as immunotoxic, endocrinotoxic, or neurotoxic. More than 50 neurotoxic chemicals are known to also be toxic to the immune system. Of these, 20 are also known to be toxic to the endocrine system. These are referenced to the Scorecard website, which contains the primary toxicity references [81]. Table 26.4 lists these chemicals.

Table 26.4 Chemicals with Multiple System Toxicities: Central Nervous (CNS), Immune (IMM), and Endocrine (END) Systems Indicated by Asterisks

Chemical	CNS	IMM	END
Acrylamide	*	*	
Acrylonitrile	*	*	
Alachlor	*	*	*
Arochlor 1254 (PCB)	*	*	*
Arsenic	*	*	*
Atrazine	*	*	*
Benzene	*	*	*
Carbaryl	*	*	*
Cobalt	*	*	
Cyclohexanone	*	*	
DDT	*	*	*
Diazomethane	*	*	
Dibenzothiazine	*	*	
Dibutyl phthalate	*	*	*
1,2-Dichlorobenzene	*	*	
Dichlorvos	*	*	
Dieldrin	*	*	*
Diethylamine	*	*	
Diethyl phthalate	*	*	*
Diethyl stilbestrol	*	*	
Diisopropyl amine	*	*	
1,4-Dioxane	*	*	
Endosulfan	*	*	*
Ethyl acrylate	*	*	
Ethylene diamine	*	*	
Ethylene oxide	*	*	
Formaldehyde	*	*	

(Continued)

Table 26.4 (Continued)

Chemical	CNS	IMM	END
Gold	*	*	
Hexylene glycol	*	*	
Hydrazine	*	*	*
Hydroquinone	*	*	
(+)-4-Isopropyl-1-methylcyclohexene	*	*	
Lead	*	*	*
Malathion	*	*	*
Maneb	*	*	*
Mercury	*	*	*
Methacrylonitrile	*	*	
Methyl acrylate	*	*	
MeHg	*	*	
Nickel	*	*	*
Ozone	*	*	
Potassium dichromate	*	*	
Propylene glycol	*	*	
Pyridine	*	*	
Styrene	*	*	*
Tin	*	*	*
Toluene	*	*	
Triethyl amine	*	*	
Xylene	*	*	
Zineb	*	*	*
Ziram	*	*	*

The chemicals that are toxic to all three systems include organophosphate, organochlorine, and carbamate pesticides, other persistent organic products, heavy metals, solvents, plasticizers, industrial chemicals, and chemicals used in consumer products.

The nitric oxide/peroxynitrite mechanism proposed for chemical sensitization illnesses [26, 50] dictates that chemicals that lead to OS in the body would exacerbate the effects by increasing nitric oxide and peroxynitrite concentrations. Many of the chemicals listed in Table 26.4 as well as other heavy metals, polyaromatic hydrocarbons, haloalkanes, aromatic amines, phenols, alkenes, alcohols, and other compounds also act [82–86]. Table 26.5 contains a partial list of these chemicals.

The chemicals listed in Tables 26.4 and 26.5 are all toxic to humans. It is hypothesized that single chemicals with multiple-organ targets in the body as well as mixtures of chemicals that together target multiple organs act to sensitize the body to chemical insult in MCS and, at the very least, act to promote symptoms in patients with CFS and FM. In the extreme, multiple-organ chemical action can be one of the agents to trigger the onset of CFS and FM, as in the case of GWS. Weight is given to this hypothesis by an examination of the products known to bring on MCS symptoms (Table 26.3) and the enhanced toxic effects attributed to mixtures. All of the

Table 26.5 Xenobiotic Chemicals Leading to Increased OS [82–86]

Lead	2,4-D
Mercury	Atrazine
Cadmium	Cyanazine
Beryllium	PCP
Arsenic	Methyl bromide
Chromium	1,2-Dibromomethane
Nickel	Ethylene oxide
Manganese	Ethanol
Iron	Octylphenol
Copper	Nonylphenol
Vanadium	Epichlorohydrin
Zinc	Styrene
Platinum	Acrylonitrile
Selenium	1,3-Butadiene
Silica	Phenol
Carbon tetrachloride	Phthalates
Chloroform	PCBs
Methylene chloride	Dioxins
TCE	Hydrogen peroxide
Benzene	Benzidine
Bromobenzene	Ethylene
DDT	VC
Methoxychlor	Vinylidene chloride
Chlorpyrifos	Potassium bromate
Acephate	2-Nitropropane
Permethrin	Tobacco smoke
Paraquat	

products in Table 26.3 are composed of mixtures of lipophilic and hydrophilic compounds. Most are toxic to the CNS, immune, and endocrine systems and many are known to induce OS. Chemical mixtures of lipophilic and hydrophilic chemicals are known to induce low-level chemical sensitivity that is enhanced via the facilitated absorption of hydrophiles by lipophiles [31].

26.9 Summary

Large numbers of causative agents, mostly mixtures of functionally different chemicals, have been associated with MCS. People with MCS exhibit a variety of reversible symptoms that are primarily respiratory, neurological, immunological, endocrine, and musculoskeletal, but other organ symptoms as well. Several mechanisms have been proposed to explain MCS, and although different from each other, these mechanisms are not mutually exclusive. Though MCS has been shown to be caused by exposures to single chemical compounds, most of the causative exposures

are to mixtures of chemicals. The causative chemical mixtures for MCS are complex, containing numerous lipophiles and hydrophiles, that include VOCs, pesticides, and other persistent organic pollutants, heavy metals, and food additives that can act synergistically. The composition of the toxic chemical “soup” to which people are exposed in modern society is also constantly changing. These variables may account for the wide range of seemingly causative agents and symptoms that have been reported for MCS.

There is evidence that CFS and FM are triggered by chemical exposure, though that is not the primary trigger. Many of the symptoms attributable to CFS and FM are similar to those in MCS and there is comorbidity among patients with these illnesses. There are mechanistic similarities between all three syndromes, i.e., increases in nitric oxide and peroxynitrite levels (increased OS). Though it has been suggested that MCS, CFS, and FM are all manifestations of the same disorder, symptoms in MCS are reversible upon withdrawal of the triggering agents, while those in CFS and FM do not readily resolve upon withdrawal of chemical stimuli.

MCS, CFS, and FM all have immune, nervous, and endocrine system manifestations. It has been hypothesized that chemicals, or mixtures of chemicals, which attack these multiple systems may be causative for the onset of all three. The fact that large numbers of Gulf War veterans, who were exposed to a multitude of chemicals toxic to all three systems and continued to demonstrate clinical symptoms for all three conditions, lend supporting evidence for this hypothesis.

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27 Skin

Chapter Outline

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27.1 Introduction

Human skin provides a barrier that protects the body from the physical, biological, and chemical environment. Skin, however, is also a permeable membrane through which xenobiotic chemicals may enter the body. Chemicals contacting the skin can also injure or burn the skin, cause dermatitis, sensitization, and other skin maladies, and make the skin less able to guard against physical and biological insult. Lipophilic chemicals more easily permeate the skin than hydrophilic chemicals, but when mixed together, the lipophiles facilitate the absorption of the hydrophiles.

As a rule, chemicals that are injurious to the skin also adversely affect the eyes and organs of the gastrointestinal and respiratory systems when contact is made. The effects on these organs are greater than those on the skin because they lack the protective layers present in the skin.

More than 800 chemicals have been identified as being toxic to the skin. These include aliphatic, aromatic, and chlorinated hydrocarbons, alcohols, esters, ethers, glycols, aldehydes, ketones, inorganic oxidizers, heavy metals, acids, alkalis, pesticides, plasticizers, polynuclear aromatic compounds, POPs, and surfactants [1–3]. A partial list of these chemicals is contained in Table 27.1. A more complete list is available on the Scorecard website.

27.2 Skin Permeability

Skin is naturally covered with protective lipophilic oils and the outer layer of the skin, the stratum corneum, is also lipophilic [4, 5, 49]. As a result, lipophilic chemicals are absorbed through skin at higher rates than hydrophilic species and

Table 27.1 Partial List of Chemicals Toxic to the Skin

Acetaldehyde	Hydrogen cyanide
Acetic acid	Hydrogen fluoride (hydrofluoric acid)
Acetone	Hydrogen peroxide
Acetophenone	Hydroquinone
Acrolein	Isopropyl alcohol
Acrylamide	Lead compounds
Aldrin	Malathion
Allyl alcohol	Maneb
Allyl amine	Mercury compounds (organic and inorganic)
Ammonia	Methacrylic acid
Ammonium dichromate	Methanol
Ammonium persulfate	Methoxychlor
Aniline	MEK
Anthracene	MIBK
Antimony compounds	Methyl isocyanate
Arsenic compounds	Methyl methacrylate
Atrazine	Methyl paraben
Benzene	Methylene blue
Benzoic acid	Methylene chloride
Beryllium compounds	Naphthalene
Biphenyl	Nitric acid
Bis(2-ethylhexylphthalate)	Nitrogen dioxide
Bismuth compounds	Oxalic acid
Bromine	Ozone
Butyl acetate	<i>p</i> -Aminophenol
Butyl alcohol	PPD
Butyraldehyde	Paraquat
Calcium hydroxide	Parathion
Calcium oxide	PCP
Carbaryl	Phenol
Carbon disulfide	Phosgene
Chloramines	Phosphoric acid
Chlorine	Phosphorus
Chromium compounds	Phthalic anhydride
Cobalt compounds	Platinum compounds
Cresol (all isomers)	PBBs
Cumene	PCBs
Cyclohexanone	Potassium hydroxide
DDT	Portland cement
Diazinon	Propionic acid
Diazomethane	Propyl paraben
Dichlorvos	Propylene glycol
Diethyl ether	Propylene glycol monomethyl ether
Diethyl phthalate	Pyrethrum

(Continued)

Table 27.1 (Continued)

Diethylene glycol	Pyridine
1,2-Dibromoethane	Selenium compounds
1,2-Dichlorobenzene	Sodium azide
1,2-Dichloroethane	Sodium carbonate
1,1-Dichloroethylene	Sodium fluoride
1,1-Dimethylhydrazine	Sodium hydroxide
Dimethyl sulfate	Sodium hypochlorite
Epichlorohydrin	Sodium metabisulfite
Epoxy resins and hardeners	Stoddard solvent
Ethanol	Styrene
Ethyl acetate	Sulfuric acid
Ethyl acrylate	Tetrachloroethylene
Ethylbenzene	Tetrasodium pyrophosphate
EDTA	Thallium compounds
Ethylene glycol	Tin compounds
Ethylene glycol monobutyl ether	Toluene
Ethylene glycol monomethyl ether acetate	TDI
Ethylene oxide	1,1,1-Trichloroethane
Formaldehyde	TCE
Formic acid	Triethanolamine
Gasoline	Triethyl amine
Glutaraldehyde	Turpentine
Gold compounds	Vinyl acetate
Heptachlor	VC
HCB	VM&P naphtha
Hexachlorophene	Xylene (all isomers)
Hydrazine	Zinc compounds
Hydrogen bromide (hydrobromic acid)	Zineb
Hydrogen chloride (hydrochloric acid)	Ziram

permeability is directly related to K_{ow} , as demonstrated by the following two studies. In the first, the permeabilities of a homologous series of parabens across excised guinea pig dorsal skin increased with increasing K_{ow} values as follows [6]:

Paraben	K_{ow}	Normalized Permeability Coefficients
Methyl	1.66	1.00
Ethyl	2.19	5.02
Propyl	2.71	10.18
Butyl	3.24	14.16

In the second study, carried out a quarter of a century earlier, it was reported that skin permeability was increased after treatment with nonpolar solvents, and that the permeability constants for a homologous series of alcohols were a function of

Table 27.2 Relationship Between Skin Permeability Constants (K_p) and Octanol/Water Partition Coefficients for a Homologous Series of Alcohols

Alcohol	K_p	K_{ow}
Methanol	1.0	−0.77
Ethanol	1.2	−0.31
Propanol	1.4	0.25
Butanol	2.5	0.88
Pentanol	6.0	1.51
Hexanol	13.0	2.03
Heptanol	32.0	2.62
Octanol	52.0	3.00

Table 27.3 Permeability Coefficients (K_p) in Human Breast Skin and Octanol/Water Partition Coefficients for THMs in Water

THM	K_p	K_{ow}
Chloroform	0.16	1.97
Bromodichloromethane	0.18	2.00
Chlorodibromomethane	0.20	2.16
Bromoform	0.21	2.40

Source: Ref. [10].

increasing carbon number [6]. What the authors of that study did not report is that the increased permeability observed corresponds exactly to increasing K_{ow} values. The data in Table 27.2 show the relationship between permeability constants (K_p) and K_{ow} values.

Organic chemicals dissolved in water, even in small concentrations, can also absorb through the skin. As was discussed in Chapter 8, drinking water in many areas is disinfected with chlorine and, as a result, DBPs containing THMs are introduced into potable water. Showering, bathing, and swimming in such water have been shown to result in the absorption of significant quantities of THMs [7–9]. In a study in which human breast skin was exposed to DBPs in water, it was found that the THM permeability through the skin correlated well with K_{ow} values [10]. The higher the K_{ow} (the more lipophilic it is), the greater the permeability. Table 27.3 shows the permeabilities and K_{ow} values for the THMs in this study.

The exposure of skin to mixtures of lipophilic and hydrophilic chemicals leads to the increased absorption of the hydrophilic species [11]. The following studies are illustrative:

1. Penetration of mouse skin was significantly increased for the herbicides atrazine, alachlor, and trifluralin in their commercial formulations compared to the herbicides alone. Lipophilic solvents were contained in all three commercial formulations [12].

2. White spirit, a mixture of mostly aliphatic (lipophilic) hydrocarbons, enhanced the penetration of the pesticide lindane through human skin [13].
3. PCP absorption in porcine skin was tripled when exposure to PCP was preceded by pre-exposure to the lipophilic PAH BaP [14].

As discussed in Chapters 11, 13, and 14, and illustrated by Refs. [15, 16], skin permeability is also enhanced by surfactants and other so-called “inert” ingredients in cleaning products, pesticides, and other chemical formulations.

Most drugs do not penetrate epithelial barriers at rates sufficient for clinical usefulness without permeability enhancers, chemicals that are routinely added to dermal drug delivery products [17]. For example, using human skin in an *in vitro* study, it was demonstrated that sodium diclofenac ($K_{ow} = 0.70$) permeability was enhanced by a mixture containing the lipophiles oleic acid ($K_{ow} = 7.64$) and D-limonene ($K_{ow} = 4.57$) [18].

27.3 Allergic Contact Dermatitis

ACD is a skin reaction resulting from dermal contact with allergens. ACD progresses in two phases. Sensitization is acquired in the initial phase. In the second phase, subsequent exposure elicits an inflammatory reaction [19]. Large numbers of chemical compounds are known to cause ACD. These include acrylates, aldehydes, amines, anhydrides, ethanolamines, formaldehyde resins, metals, pesticides, phenols, phthalate esters, preservatives, isocyanates, solvents, and others. One skin sensitizer, PPD, which is used as an additive to henna in hair dyes and in skin coloring, is a delayed type skin sensitizer whose sensitizing effects are not immediately experienced [20, 21].

Table 27.4 contains a partial list of skin sensitizing chemicals. A more complete list can be found on the web [22].

ACD has been associated with ethoxylated alcohol surfactants. Though not by themselves known to cause ACD, ES are polyethers and are easily air oxidized to hydroperoxides, peroxides, and carbonyl compounds (including formaldehyde and acetaldehyde), substances that do cause ACD [23–26]. The irritant components of surfactants and other chemicals present in formulated products facilitate the absorption of the ACD-causing decomposition products of ethoxylated alcohols and thus exacerbate their effects [27]. This is yet another example of lipophilic compounds enhancing the absorption of hydrophilic compounds (the decomposition products of ethoxylated alcohols) and hence increasing the toxic effect beyond that predicted.

The *in situ* formation of contact dermatitis-producing chemicals is not limited to ethoxylated alcohol degradation. Photocontact allergic dermatitis can be caused by the application of photosensitive chemicals to the skin followed by irradiation with UV light [28]. Examples of such reactions were discussed in Section 16.4.

Combinations of allergens have been shown to produce synergistic effects in sensitized individuals. A study was made in which 18 human volunteers with contact allergies were exposed to a 1:1 mixture of two fragrance compounds, each of which is known to induce ACD. The mixtures elicited responses that were 3–4 times higher than anticipated from an additive effect [29]. No mechanistic explanation was offered by the authors of the study.

Table 27.4 Compounds Known to Cause ACD

Acrylic acid	Maneb
Methacrylic acid	Zineb
Methyl methacrylate	Methylene bisphenyl isocyanate
Formaldehyde	TDI
Acetaldehyde	Hexamethylene diisocyanate
Glutaraldehyde	Chromium
Cinnamic aldehyde	Nickel
Ethylene diamine	Mercury
Triethanolamine	Cobalt
Toluene diamine	D-Limonene
Diphenyl amine	Turpentine
Triethanolamine	Diethyl phthalate
Acetic anhydride	Dibutyl phthalate
Maleic anhydride	Benzalkonium chloride
Phthalic anhydride	Hexachlorophene
PPD	Hydrazine sulfate
Ammonium persulfate	Benzoyl peroxide
Glyceryl monothioglycolate	Cyanamid
Ammonium thioglycolate	Dioxane
Epichlorohydrin	Propylene glycol
Bisphenol A	Triphenyl phosphite
Carbaryl	

Source: Ref. [22].

27.4 Dermally Induced Respiratory Hypersensitivity

Sensitization of the respiratory tract may result from dermal contact with a sensitizing chemical [30–32]. Several studies have made this association for chromate [33], latex [34], the herbicide 3-amino-5-mercapto-1,2,4-triazole [35], and trimellitic anhydride, which is a respiratory sensitizer when inhaled [36, 37].

The reverse phenomenon has also been demonstrated. Isolated airway exposure to TDI, a powerful respiratory sensitizer, has been demonstrated to cause skin sensitization [38]. These crossovers are believed to be due to the observation that both dermal and respiratory sensitization result in increased serum IgE antibody levels [32, 34] and point out the dangers associated with exposures to sensitizing chemicals.

27.5 Chemical Burns

Chemical burns result when living tissue makes contact with corrosive chemicals. Though most chemical burns are to the skin, eye contact, ingestion, and inhalation of corrosives also result in numerous chemical burn instances. It is important to differentiate between chemical irritation and burning. Chemical irritants produce reversible reactions that include swelling, itching, and burning sensations. These effects, however,

are transient and skin returns to its normal state when the irritating agent is removed. Chemical burns, on the other hand, are irreversible and result in permanent injury.

Substances that cause chemical burns include acids, alkalis, solvents, and oxidizing and reducing agents. Most chemical burns (including those caused by acids) act by denaturing proteins on contact and producing coagulation necrosis. Alkalis liquefy tissue via denaturalization of proteins and saponification of fats, causing liquefaction necrosis. In acid burns, penetration into tissue is limited by coagulation, thus limiting the damage. Alkali burns, which do not cause coagulation, continue to penetrate very deeply into tissue [39]. This phenomenon makes alkali burns potentially much more dangerous, since the burns do not always immediately produce symptoms, but are progressive over time, producing extensive tissue destruction. Alkali burns are, accordingly, also referred to as progressive burns. It should be noted that hydrofluoric acid is unique among acids, in that it, like alkalis, produces a liquefaction necrosis, making it perhaps the most dangerous acid for skin contact.

Most chemical burns are caused by acid or base contact.

Acid sources include:

Drain cleaners containing hydrochloric or sulfuric acid.

Tile cleaners containing hydrochloric, sulfuric, sulfamic, or phosphoric acids.

Automobile battery fluid containing sulfuric acid.

Engraving fluids containing nitric acid.

Etching solutions containing hydrofluoric acid [40, 41].

Alkali sources include:

Oven cleaners containing sodium or potassium hydroxide.

Household detergents (laundry and dishwashing) containing sodium silicates or sodium carbonate.

Drain cleaners containing sodium or potassium hydroxide.

Cement, mortar, or plaster containing calcium hydroxide or oxide [42, 43].

Chemicals that are burn agents include:

Anhydrous ammonia [44]

Sodium azide (found in automobile air bags) [45]

Organic solvents (including toluene) [46, 47].

In short, it is to be anticipated that any solution with a pH greater than 10.0 (alkaline) or less than 3.0 (acidic) has the potential to cause chemical burns. The higher the acidity or alkalinity of a solution, the greater burn danger it poses. Oxidizing and reducing agents, e.g., chromates, chlorine, and hydrazine, also pose burn dangers that increase with concentration.

27.6 Mixtures

Most instances of skin reactions to chemical mixtures can be attributed to single components of the mixtures. There are, however, exceptions and most are due to the use of formulated products containing surfactants. These products include household and

industrial cleaners, cosmetics, and hair treatments. Surfactants contribute to adverse dermal reactions by stripping the oils which protect the skin, leaving the skin more vulnerable to attack by other chemical species. For example, it was found in one study that the simultaneous application of known contact allergens and a surfactant, sodium lauryl sulfate, to the skin results in an enhanced response to the allergens [48].

Chemical burning by alkalis is also enhanced when the alkaline products also contain surfactants. In a case study investigated by this writer, a woman received severe progressive chemical burns on her hands when she mixed two cleaners together, one containing sodium carbonate and sodium percarbonate and the other containing the surfactants sodium dodecylbenzene sulfonate and sodium lauryl ether sulfate. Though each product is considered to be safe for dermal contact, the mixture burned the user's skin. In this instance, it is believed that the surfactants stripped the protective oils, allowing the alkali to penetrate and burn the skin.

Solvent mixtures can also cause chemical burns. Numerous cases one paper reports on five such incidences [49].

27.7 Summary

The human skin serves as the body's first line of defense against biological and chemical attack. It is not, however, an armored plate. Rather, it is a permeable membrane that is vulnerable to attack by a large number of chemicals. It is subject to irritation and burning by chemicals and can also react to chemical allergens, as in ACD. Respiratory sensitization can also ensue following dermal sensitization.

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28 Musculoskeletal System

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28.1 Introduction

Xenobiotic exposure can adversely affect bones, joints, connective tissue, and muscles. Rheumatoid arthritis (RA), osteoporosis, osteomalacia, systemic sclerosis (SS), scleroderma (SSc), SLE, and spina bifida are musculoskeletal diseases that have been associated with toxic chemical exposures. Most of these associations, however, have been made to single chemical exposures and not mixtures. This chapter will cite the evidence on which those associations are based and discuss the available examples of mixtures that have been implicated.

Chemicals that are toxic to the musculoskeletal system are listed in Table 28.1 [1–7].

Table 28.1 Musculoskeletal Single Chemical Toxins

Aluminum	Phosphine
Arsenic	Phosphorus
Benzene	Selenium
Carbaryl	Silica
Cadmium	Sulfuric acid
Chlorobenzene	Tetrachloroethylene
Chloroform	Toluene
Disulfiram	Toluidine
Ethanol	1,1,1-Trichloroethane
Fluorides	TCE
Hydrochloric acid	Xylene
Hydrofluoric acid	Xylidine
Lead	

28.2 Rheumatoid Arthritis

RA is a chronic inflammatory disease that affects connective tissue, particularly the linings of the joints (synovium). Exposure to respirable dust, particularly silica (but including agricultural and organic dust), has been shown to produce a dose–response relationship with RA [6, 8–10]. Miners, farmers, pulp and paper workers, textile workers, millers, and bakers all have higher incidences of RA than the general public. It is unknown if the inhaled dusts are either antigenic alone or act as immunological adjuvants that enhance the inflammatory responses of other causative agents [8].

28.3 Scleroderma and Systemic Sclerosis

SSc is a chronic autoimmune disease characterized by excessive deposition of collagen and fibrosis (formation of scar tissue) in the skin and other body organs. Though the local manifestation of this disease is not serious, SS, the serious manifestation, can be fatal. Since exposures to the same chemicals have been associated with both variants of this disease, they will be discussed together.

Occupations that are associated with SSc and SS include those where exposures to organic solvents and silica are common [1, 11–14]. A partial list of these occupations is given in Table 28.2 [1, 11–14], and a list of the chemicals which have been associated with SSc and SS is given in Table 28.3 [1, 9, 13–19].

Table 28.2 Partial List of Occupations Associated with SSc and SS

Arts and crafts	VC manufacturing
Adhesive manufacturing	Cosmetic and perfume manufacturing
Paint manufacturing	Pathology laboratory work
Painting	Fiberglass manufacturing and use
Furniture refinishing	Leather tanning
Plastics manufacturing	Shoe manufacturing
Petroleum refining	Professional cleaning and maintenance
Hair dressing	Construction

Table 28.3 Partial List of Chemicals Associated with SSc and SS

Benzene	Tetrachloroethylene
Cleaning products	Toluene
Chloroform	Toluidine
Diesel fuel	1,1,1-Trichloroethane
Epoxy resin catalysts	TCE
Gasoline	VC
Mineral spirits (Stoddard solvent)	VM&P naphtha
Paint removers	Xylene
Paint thinners	Xylidine
Silica	

All the occupations listed in Table 28.2 carry with them exposures to mixtures of lipophilic and hydrophilic chemicals. Of the chemicals listed in Table 28.3, several are mixtures of compounds. These include gasoline, diesel fuel, mineral spirits, paint removers, paint thinners, and varnish makers and painters (VM&P) naphtha. Though many of the studies referenced earlier consider organic solvents as only a mixture of lipophilic compounds [13–15, 17], this is inappropriate, since many of the chemicals listed in Table 28.3 are mixtures of lipophiles and hydrophiles. For example, a typical solvent-based paint remover contains the following components (K_{ow} values are listed to demonstrate lipophilic or hydrophilic properties):

Chemical	K_{ow}
Acetone	−0.24
Methanol	−0.77
Methylene chloride	1.25
Toluene	2.78

As was seen in Chapter 11, paints, art and craft supplies, adhesives, and cleaning products are also composed of mixtures of lipophiles and hydrophiles.

The evidence for ascribing environmental exposures as being causative for SSc comes from the following consideration. Though women in the general population are predominantly afflicted with SSc, among those with occupational exposures to organic solvents, men are at higher risk for the disease than women [11]. It has been suggested that solvent induction of SSc is due to the triggering of an autoimmune response in susceptible individuals via enzymatic binding to these solvents [17].

28.4 Systemic Lupus Erythematosus

SLE is a chronic autoimmune connective tissue disease characterized by inflammation and injury to the joints, tendons, and other connective tissues. Organs affected include lungs, heart, blood vessels, brain, kidneys, and skin. SLE onset is associated with exposure to silica. Though earlier studies have suggested that organic solvent exposure can also be causative for SLE, more recent studies have refuted this [2, 3, 9]. No literature references were found associating SLE onset with exposures to chemical mixtures.

28.5 Osteoporosis and Osteomalacia

Exposures to toxic chemicals can adversely impact the bones as well as the soft tissues of the body. Osteoporosis and osteomalacia are two examples of this effect.

Osteoporosis is a condition characterized by a loss of bone mass and density that has been causally related to exposure to cadmium, a toxic heavy metal that is widely distributed in the ambient environment. In a Chinese study, a dose–response relationship between cadmium exposure and osteoporosis was demonstrated [4].

Other studies have demonstrated that exposure even to low levels of cadmium is associated with an increased risk of osteoporosis [20, 21].

Osteomalacia is a condition in which the bones are softened due to impaired mineralization. Exposure to cadmium has been found to be causative for osteomalacia [20, 22, 23]. Other chemicals associated with osteomalacia are aluminum, lead, and fluoride [24].

28.6 Mixtures

Only a very few studies have documented the toxic effects of chemical mixtures on the musculoskeletal system. Almost all of these studies address the effects of tobacco smoking and organic solvent exposure. The following studies are illustrative of those reported:

1. A study in 1994 reported that tobacco smoking is the only environmental exposure risk factor that has been associated with RA. The authors of the study concluded that tobacco smoke can "reasonably be regarded as a contributory cause of RA" [25]. No specific compounds in tobacco smoke were identified as being causative and no mechanism for the action of such smoke was offered.
2. Cigarette smoke has harmful effects on a number of orthopedic conditions. It delays the healing process associated with both bone fracture and ligament injury. In a study carried out on laboratory mice it was shown that cigarette smoking retarded the healing of a collateral ligament injury [26]. A companion study demonstrated that smoke also delays the healing of broken tibias and the development of mature cartilage cells [27].
3. In a study of men with symptomatic osteoarthritis, those who smoke were found to have the disease be more progressive to sustain more than twice the cartilage loss and have more severe pain than their nonsmoking cohorts. This despite the observation that the smokers in the study were younger and thinner than the nonsmokers, factors that normally reduce the effects of osteoarthritis [28].
4. In a case study, a 56-year-old man developed SS after 23 years of work in a tire manufacturing factory. The chemicals he was exposed to included:
Toluene
Heptane
Dimethylbutylphenyldiamine
Octylphenol formaldehyde.
The man was exposed via inhalation and dermal routes. His SS developed progressively over 8 years to the point where he had skin, lung, and pericardial involvement [29].
5. In another case study, a 26-year-old woman was diagnosed with skin SSc following a 1-year exposure to solvent vapors that included:
TCE
Tetrachloroethylene
Acetone
Benzene
Isopropanol
Dimethyl phthalate
Methoxyethanol
Phenol
Xylene [30].

6. In a study involving more than 600 patients with SSc, statistically significant associations were found between SSc and exposures to paint thinners and paint removers [17].
7. Undifferentiated connective tissue disease (UCTD) is a term used to describe conditions where people have symptoms and laboratory test results that resemble known musculoskeletal diseases such as SS and SSc but do not have enough of the symptoms to meet the requirement for a well-defined diagnosis of a single disease. A study of patients with UCTD found statistically significant associations with exposures to paint thinners and paint removers [31].

As discussed earlier, paint removers are mixtures of lipophilic and hydrophilic chemicals formulated together to ensure maximum attack on paint. Paint thinners are generally composed of VM&P naphtha and mineral spirits. VM&P naphtha is a mixture of aliphatic alkanes and alkenes and aromatic hydrocarbons. Mineral spirits is a higher molecular weight composition of similar compounds.

28.7 Summary

Musculoskeletal diseases that are triggered by exposures to xenobiotics include connective tissue and bone moieties. These effects are generally observed after long-term exposures to toxic chemicals, including heavy metals and organic solvents. The long period of time following initial exposure until the onset of symptoms complicates the study of chemically induced musculoskeletal disease and makes the effects of chemical mixtures difficult to assess. As a result, only a relatively few studies in this area have been carried out. Those that have been carried out have demonstrated the musculoskeletal toxicity of single chemicals, e.g., TCE, and suggested an effect of chemical mixtures.

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29.1 Introduction

Cardiovascular toxins are those chemicals that are toxic to the heart, blood vessels, and blood. More than 500 individual chemicals fall into this category. Table 29.1 contains a partial list of these compounds. A more complete list, along with primary references, is available on the Scorecard website [1].

It is beyond the scope and outside the intended purpose of this book to explore the individual cardiovascular toxicities of these compounds. The following, however, are a few examples of these.

Arteriosclerosis, commonly called hardening of the arteries, is a hardening and thickening of the arterial walls resulting in loss of elasticity. Atherosclerosis is a form of arteriosclerosis characterized by the deposition of plaques on the innermost layers of large- and medium-sized arteries. 1,3-Butadiene, widely used as a monomer in the rubber and plastics industries and a component of cigarette smoke, has been shown to accelerate the development of atherosclerosis by promoting plaque development [2, 3].

Intentional inhalation, or “huffing,” of VOCs for the purpose of inducing euphoria can bring on cardiac arrhythmia, ventricular fibrillation, myocardial infarction, cardiac arrest, and dilated cardiomyopathy, a condition in which the heart becomes enlarged and weakened, thereby limiting its ability to pump blood [4–15]. Table 29.2 contains a list of cardiotoxic chemicals frequently intentionally inhaled and their common sources.

The chemicals in Table 29.2 are often inhaled as mixtures. Though there are surely at least additive effects associated with many of these mixtures, there is evidence that each of these alone is toxic to the heart.

Table 29.1 Partial List of Chemicals Toxic to the Cardiovascular System

Acetanilide	Ethanol
Acetone	Ethylbenzene
Acetonitrile	Ethylene glycol
Alachlor	Ethylene glycol monoethyl ether
Allyl alcohol	Formic acid
Aluminum	Hydrogen cyanide
Ammonium nitrate	Hydrogen sulfide
Ammonium dichromate	Isopropanol
Aniline	Lead
Arsenic	Manganese
Barium carbonate	Mercury
Benzene	Methyl chloride
Bismuth	MEK
Boron	Methyl mercuric chloride
1,3-Butadiene	Methyl methacrylate
Cadmium	Methyl parathion
Carbon disulfide	Methylene chloride
Carbon monoxide	Naphthalene
Carbon tetrachloride	Parathion
Chlordane	PCBs
Chlorine	PCP
Chloroacetic acid	Phenol
Chlorofluoromethanes	Sodium azide
Chloroform	Sodium hypochlorite
Cobalt	Sodium perchlorate
Copper	TCDD
Cyanide	Tetrahydrofuran
Cyclohexanol	Toluene
DDT	Toluene-2,4-diisocyanate
Dieldrin	1,1,1-Trichloroethane
Dinitrophenols	Xylenes
Diphenyl amine	Zinc
Endrin	

TCE and its metabolite TCA are cardiac teratogens. Both are common drinking-water contaminants in the United States, and exposure to TCE during pregnancy has been shown to produce congenital heart defects in children exposed to it in utero via an unknown mechanism. The risk for congenital heart defects in children whose mothers lived in close proximity to TCE-emitting sites is 3 times more than those whose mothers were not so exposed [16–18].

Exposures to pesticides produce multiple systemic effects [19]. Exposure to the organophosphate methyl parathion can cause cardiac arrest as well as neurological and respiratory effects [20].

Table 29.2 Chemicals Frequently Abused by Intentional Inhalation That Induce Cardiac Arrhythmia, Cardiac Arrest, or Cardiomyopathy

Chemical	Source
Acetone	Nail polish remover, rubber cement, marking pens
BCDFM and other fluorocarbons	Fire extinguishers, spray paints, hairsprays, room fresheners
Butanes	Cigarette lighter fluid
Ethyl acetate	Glues
Aliphatic hydrocarbons	Gasoline
Aromatic hydrocarbons	Gasoline
Propane	Grill fuel
Toluene	Paints, paint thinners, glues
1,1,1-Trichloroethane	Correction fluid, spot removers

Neovascularization, the formation of new blood vessels, is an essential life process. TCDD interferes with neovascularization by inhibiting the formation of new capillary sprouts from pre-existing vessels (angiogenesis) [21].

Heavy-metal exposures are well known to impact the cardiovascular system. Workers exposed to manganese have been found to have accelerated heart beats and mean diastolic heart blood pressures that are significantly lower than those of controls [22]. Mercury and cadmium exposures are associated with hypertension, vascular disease, and myocardial infarction (heart attack) [23]. There is a causal relationship between lead exposure and hypertension [24].

From Table 29.1, it is obvious that chemicals with many different functional groups are cardiovascular toxins. These include hydrocarbons, chlorinated hydrocarbons, ketones, pesticides, heavy metals, and others. A unifying mechanism for the action of these far different chemicals has been proposed. This mechanism is based on a consideration of OS and postulates that chemicals or their metabolites that give rise to ROS that are formed by ET may be cardiovascular toxins [25]. The ET–OS–ROS mechanistic perspective has been used to account for the cardiotoxicity of the chemicals listed in Table 29.3 [25].

It is interesting to note that nitric oxide, an endogenous chemical associated with numerous essential biochemical processes in the body [16], is included in this list of cardiovascular toxins. Excessive nitric oxide is associated with arterial disease including atherosclerosis [26–29, 58].

Relatively few studies have been carried out on the toxic effects of chemical mixtures on the cardiovascular system. The research that has been published addresses the effects of nonspecific mixtures, including landfill leachates, air pollution, and tobacco smoke. These are discussed in the following three sections.

Table 29.3 Chemicals Cardiotoxic via ET–OS–ROS Mechanism

Acrolein	Manganese
Allyl amine	Mercury
Arsenic	3,4-Methylenedioxymethamphetamine
1,3-Butadiene	Nickel
Cadmium	Nicotine
Chromium	Nitric oxide
Cobalt	<i>N</i> -Nitrosamines
Cocaine	Paraquat
Copper	PCBs
Dioxins	Phenyl hydrazine
Ethanol	Silicates
Lead	Vanadium
Lindane	

29.2 Leachates

Landfill leachates contain many of the compounds listed in Table 29.1 and would, therefore, be expected to show cardiovascular toxicity. Only one study was found in the literature that specifically addresses the cardiotoxicity of landfill leachates. The results of that study are as follows.

Leachates from landfills have complex and variable compositions, often making it difficult to ascribe particular effects arising from exposure to these. Leachates from sources containing well-defined chemical compositions can be studied more accurately. In a recently published study, an *in vitro* examination of human peripheral blood lymphocytes demonstrated the effect of three different leachates on the induction of DNA damage. Polyfiber factory, aeronautical plant, and municipal sludge leachates all induced significant concentration-dependent increases in DNA damage compared with control [30]. It is interesting to note that although the compositions of three leachates varied widely, all affected DNA. This study pointed out the sensitivity of human blood to a wide variety of toxic chemicals.

29.3 Air Pollution

Several studies have definitively demonstrated that breathing polluted air is associated with cardiovascular disease [31–39]. Prior to addressing these studies, let us examine the chemical composition of polluted air.

As was discussed in Chapter 7, polluted air varies in composition from locale to locale and with the time of day and meteorological conditions in a given locale. Polluted urban air contains oxides of sulfur and nitrogen, carbon monoxide, ozone, uncombusted and partially combusted hydrocarbons from gasoline and diesel vehicles, and particulate matter. PM_{2.5} particulates, the standard for evaluating pollution

Table 29.4 Composition of Urban PM_{2.5} Particles and Their Sources

Combustion products

Diesel fuel
Aviation fuel
Gasoline
Incineration
Structural fires
Residential wood burning
Utility power generation
Home-heating fuel
Commercial fuel

Sulfates

Oil- and coal-fired utilities
Diesel vehicles
Commercial heaters and boilers
Reaction with airborne SO_x

Nitrates

Gasoline vehicles
Diesel vehicles
Home-heating fuel
Commercial and home heaters and boilers
Reaction with NO_x

Soil

Dust from paved and unpaved roads
Construction dust

Heavy metals

Utility power generation
Industrial processing
Smelting
Mining
Airborne soil

related to cardiovascular disease, are composed of combustion products, airborne soil, sulfates, nitrates, and heavy metals as listed in Table 29.4 [40–44].

Particulate air pollutants are classified into the following three categories [34]:

- a) *<10 μm in diameter (PM₁₀)*: These particles can readily penetrate and deposit in the tracheobronchial tree.
- b) *<2.5 μm in diameter (PM_{2.5})*: These particles are small enough to reach the small airways and alveoli.
- c) *<0.1 μm in diameter, ultrafine particles*: These particles demonstrate very high deposition in human alveoli and have very high surface areas (relative to mass) which can lead to biological toxicity. These particles are small enough to penetrate protective membranes and enter the bloodstream, from where they can be deposited all over the body.

Table 29.5 Cardiovascular Diseases Whose Onset of Exacerbation Have Been Ascribed to Breathing Polluted Air

Myocardial infarction
Arrhythmia
Heart failure
Cardiac arrest
Ischemic heart disease
Atherosclerosis
Hypertension

Several of the studies, relating cardiovascular disease with air pollution, associate increases in disease with increasing quantities of PM_{2.5} [32–34, 38, 39]. It has been shown that each increase of 10 µg/m³ of PM_{2.5} was associated with a 24% increase in the risk of a cardiovascular event [39].

PM_{2.5} particulate concentration is a readily measured indicator of air pollution levels. It must be noted, however, that increases in PM_{2.5} levels invariably lead to concurrent increases in air pollutant vapors, including carbon monoxide, ozone, nitrogen dioxide, sulfur dioxide, hydrocarbons, and VOCs that arise from many of the same sources as PM_{2.5} particles. The pollution “soups” that people are regularly exposed to contain numerous lipophilic and hydrophilic compounds in addition to the particulate matter. Accordingly, though PM_{2.5} serves as an indicator of pollution levels and has been associated with cardiovascular disease, one must take into consideration the non-particulate vapors when ascribing adverse toxic effects, especially since the vapors are, by themselves, toxic to the cardiovascular system. As was discussed in Chapter 7, mixtures of air pollutants can have synergistic effects.

Both short- and long-term cardiovascular toxicity from exposure to polluted air has been reported [34, 39]. Table 29.5 lists the cardiovascular diseases whose onset or exacerbation have been ascribed to breathing polluted air [31–36, 38, 39].

Women exposed to air pollutants (as indicated by PM_{2.5} and PM₁₀ levels) are at greater risk for developing cardiovascular diseases than men. This was demonstrated in a 22-year-long cohort study of more than 3000 non-Hispanic white adults in California [36]. No explanation has been offered for the observed gender effect.

The cardiovascular toxicity of the chemicals contained in air pollutants is enhanced by the presence of free radicals in PM_{2.5} particles. Electron paramagnetic resonance has shown large quantities of free radicals in these particles with characteristics similar to semiquinone radicals, moieties known to undergo redox reactions which ultimately produce hydroxyl radicals [45]. Hydroxyl radicals contribute to the ET–OS–ROS chain of events [25].

A recent study has provided insight into the association of ambient air pollution with increased cardiovascular morbidity and mortality. In this study, when human microvascular endothelial cells were exposed to a combination of ultrafine diesel-exhaust particles and oxidized lipid components, a synergistic effect on the expression profiles of several gene modules that correspond to pathways relevant to

inflammatory pathways such as atherosclerosis was observed [46]. The implications of this study include a greatly increased risk of heart disease in those with high cholesterol who breathe polluted air.

29.4 Tobacco

It is estimated that about 1 billion people will die of tobacco-related illnesses in the twenty-first century and that a substantial proportion of these deaths will result from tobacco-induced cardiovascular disease [47]. Cardiovascular diseases associated with tobacco use include [48, 49]:

- Myocardial infarction
- Atherosclerosis
- Hypertension
- Peripheral arterial disease
- Aortic aneurism.

Tobacco exposure is toxic to the cardiovascular system, even at low levels, in all forms, including [49]:

- Cigarettes
- Cigars
- Pipes
- Smokeless (chewing tobacco and snuff)
- Beedies (a small amount of tobacco wrapped in temburni leaf and string-tied)
- Sheesha (oriental water pipe)
- Paan (a tobacco preparation used with lime, areca nut, or betel quid)
- Secondary as well as primary smoke exposure.

In a worldwide study of 27,000 people in 52 countries, 12,400 patients who experienced acute myocardial infarction (AMI) were compared with 14,000 who never had a heart attack or any other form of cardiovascular disease [49]. The study concluded the following:

1. Smoking triples AMI risk.
2. Light smoking (eight cigarettes per day) doubles the risk of AMI.
3. Light smokers who quit smoking return to nonsmokers' risk for AMI after 3–5 years.
4. Heavy smokers (more than 20 cigarettes per day) who stop smoking return to nonsmokers' risk for AMI after 20 years.
5. Exposure to secondhand smoke for 22 h per week increases AMI risk by 45%.
6. Tobacco in any form is harmful and increases the risk for AMI.
7. The increased risk of AMI associated with the use of nonsmoking as well as smoking tobacco is indicative of the presence of cardiotoxins in tobacco itself and is not confined to the combustion products of tobacco.
8. The mechanism(s) for AMI induction by tobacco remains unknown.

Even short low-level exposures to secondhand smoke are believed to increase the risk of AMI [50]. This was dramatically demonstrated in an inadvertent experiment

that was carried out in Helena, Montana in 2002. Helena, a geographically isolated community, imposed a public smoking ban on June 5, 2002. Opponents of the ban successfully won a court order suspending enforcement of the ban on December 3, 2002. During the time the ban was in effect, the number of AMIs observed in the local hospital fell by 40% compared to those observed during the 5-year period immediately preceding the public smoking ban. Immediately following the suspension of the smoking ban, the AMI number returned to its previous, pre-ban, level [51]. A citywide smoking ban in Pueblo, Colorado, another isolated community, produced results similar to those reported for Helena, Montana [52]. A third smoking-banned study in northern Italy also showed a reduction in AMI hospital admissions when a smoking ban was enacted [53]. Other studies in Italy, Ireland, Scotland, and other American cities have found similar reductions in AMI following smoking bans [54]. These studies clearly demonstrated the direct relationship between tobacco and smoke, both via actually smoking and secondhand smoke exposure, to AMI.

The combined use of tobacco with other chemicals and pharmaceuticals can have synergistic effects. For example, women who smoke and use oral contraceptives have a much greater risk for myocardial infarction than nonsmokers [55], and cigarette smoking and elevated serum cholesterol have a synergistic effect on coronary heart disease morbidity and mortality [56].

The cardiovascular toxicity of tobacco is not limited to AMI. For example, tobacco smoke inhibits neovascularization [21] and promotes arteriosclerotic plaque development [57].

29.5 Cancer

The most common form of cardiovascular cancer is leukemia. This will be addressed in Chapter 32.

29.6 Summary

The cardiovascular system is adversely impacted by many single chemicals and also by mixtures. The mixtures most toxic to the cardiovascular system are polluted air and tobacco smoke, mixtures for which relationships are so well defined that predictions can be made mathematically on the numbers of exposed individuals who will be impacted by cardiovascular disease following exposure.

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30 Liver

Chapter Outline

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30.1 Introduction

The liver is subject to attack by xenobiotics because it is the body's principal metabolic site and is the recipient of ingested toxins that travel to it from the small intestine via the portal vein. The liver is impacted by a large number of chemicals encompassing multiple functional groups that include numerous lipophiles and hydrophiles. Table 30.1 lists hepatotoxins by chemical category and Table 30.2 contains a partial list of hepatotoxins. The references cited are web sources that are referenced to primary sources for more detail [1, 2].

Hepatotoxicity for most chemical toxins mechanistically proceeds via free radical formation which causes OS that induces lipid peroxidation, membrane damage, and altered enzyme activities, the generation of ROS and hydrophilic toxins. Ethanol,

Table 30.1 Chemical Categories of Hepatotoxins

Alcohols	Esters
Aliphatic hydrocarbons	Ethers
Aliphatic nitro compounds	Glycol ethers
Amines	Halowaxes
Aliphatic	Metals
Aromatic	Nitrosamines
Heterocyclic	Pesticides
Aromatic hydrocarbons	Chlorophenoxy
Aromatic nitro compounds	Organochlorine
Chlorinated aliphatic compounds	Pyrethroids
Chlorinated aromatic compounds	Phenols
Chlorofluorocarbons	Thiols

Table 30.2 Partial List of Hepatotoxic Chemicals

Acetic acid	Ethylene oxide
Acetone	Formaldehyde
Acrolein	Formic acid
Acrylonitrile	Glyphosate
Aldrin	HCB
Allyl alcohol	Hexachloropentadiene
Aniline	Hydrazine
Anthracene	Hydroquinone
Antimony	Isopropanol
Arsenic	Lead
Atrazine	Lindane
Benzene	Malathion
Benzidine	Mercury
Benzyl bromide	Methanol
Beryllium	MEK
Biphenyl	MIBK
Bromium	Methylene dianiline
Carbon tetrachloride	Mirex
Chloroform	Naphthalene
Copper	Oxalic acid
2,4-D	Paraquat
DDE	PCBs
DDT	PCP
Diazinon	Phenol
1,2-Dichlorobenzene	Phosphine
1,1-Dichloroethylene	Potassium permanganate
1,2-Dichloroethylene	Sodium nitrite
Dichlorvos	Styrene
Diethyl phthalate	2,4,5-T
Dimethyl acetamide	Tetrachloroethylene
Dimethyl amine	Tetrahydrofuran
DMF	Thallium
Dimethyl sulfate	Thioacetamide
1,4-Dioxane	Tin
Diquat	Toluene
Endosulfan	Toluene-2,4-diisocyanate
Endrin	1,1,1-Trichloroethane
Ethanol	TCE
Ethyl acrylate	Vinyl acetate
Ethyl benzene	Xylenes
1,2-Ethylene diamine	Zineb
Ethylene glycol	Ziram
Ethylene glycol monobutyl ether	

carbon tetrachloride, and other haloalkanes are examples of chemicals that are thus hepatotoxic [3–10]. Some xenobiotics, e.g., bromobenzene, allyl alcohol, and diethylmaleate, are glutathione-depleting agents. With these, necrosis is accompanied by lipid peroxidation that develops only after severe glutathione depletion [11].

30.2 Single Chemical Hepatotoxins

Numerous studies have been carried out on the effects of single chemicals on the liver, of which ethanol and carbon tetrachloride are the most notorious [4, 8]. Other hepatotoxic chemicals, however, have also been widely studied, both in the laboratory and environmentally. For example, an outbreak of toxic liver disease was reported in a fabric coating company. Upon investigation, it was found that DMF, a known hepatotoxin, was used as a coating solvent in poorly ventilated areas without appropriate skin protection and no other hepatotoxins were identified [12].

Our discussion here is dedicated to the unexpected effects of toxic chemical mixtures. For information on identified or suspected single hepatotoxic chemicals, it is suggested that the reader carry out a literature search for the specific species of interest.

30.3 Hepatotoxic Mixtures: Animal Studies

Many laboratory animal studies have been carried out on the liver toxicity of halogenated hydrocarbon mixtures, with most of these devoted to the potentiation of carbon tetrachloride hepatotoxicity. Other studies have included heavy metals, disinfection by-products, and simulated polluted groundwater. The following points reference these studies:

1. Mixtures of the polybrominated biphenyls, PCBs, or HCB and carbon tetrachloride synergistically increase the toxic effects of carbon tetrachloride on the livers of rats [13].
2. The co-administration of the insecticide chlordecone and carbon tetrachloride potentiates the hepatotoxicity of carbon tetrachloride in laboratory animals [14, 15].
3. Hypoxia potentiates the carbon tetrachloride hepatotoxicity in animals and in humans [16].
4. TCE, tetrachloroethylene, and chloroform potentiate carbon tetrachloride-induced lipid peroxidation in isolated rat hepatocytes [17, 18].
5. Methylene chloride is not hepatotoxic at low levels of exposure, yet co-administration with carbon tetrachloride significantly potentiates the hepatotoxicity of carbon tetrachloride [19].
6. Interactive hepatotoxicity was demonstrated by the concurrent administration of mixtures of any two or all three of the chlorinated hydrocarbons TCE, tetrachloroethylene, and 1,1,1-trichloroethane. All binary mixtures as well as the ternary mixture significantly increased hepatotoxicity in vitro on rat hepatocytes as well as in vivo on laboratory rats [20].
7. Chlordecone potentiates the hepatotoxic effects of chloroform. Studies on laboratory rats showed that administration of only a single dose of chlordecone significantly potentiates chloroform-induced liver injury [21].
8. Mixtures of cadmium chloride and chloroform trigger toxic responses in isolated rat hepatocytes at concentrations sufficiently low so as not to produce a hepatotoxic response for either chemical alone [22].
9. As has been discussed earlier, chloroform and dichloroacetic acid are formed as by-products when drinking water is chlorinated (Section 8.9). In a study on laboratory rats, the co-administration of dichloroacetic acid and chloroform was found to greatly increase the liver toxicity of chloroform [23].
10. In a study carried out by the U.S. National Toxicology Program, laboratory animals were watered with water containing a mixture of 25 common groundwater contaminants at environmentally relevant levels. The chemicals, which included many lipophiles and hydrophiles, included aromatic hydrocarbons, chlorinated hydrocarbons, and other

pollutants. Exposed animals developed inflammatory lesions of the liver which could not be predicted from the known toxic effects of the individual components of the mixture at the levels the animals were exposed to. Table 30.3 lists the chemicals in the mixture [24].

11. Exposures to hydrocarbon mixtures have been shown to produce hepatotoxic effects. JP-8 jet fuel is a complex mixture of hydrocarbons, including the following volatile compounds:
- Butyl benzene
 - Cyclo-octane
 - Decane
 - Dodecane
 - Hexadecane
 - Iso-octane
 - Methylcyclohexane
 - 1-Methylnaphthalene
 - Tetradecane
 - Tetralin
 - Xylenes.

In a laboratory study, rats exposed by whole-body inhalation to JP-8 vapor experienced altered liver protein profiles, demonstrating alterations in functional capacity of the exposed animals [25].

12. Acetaminophen is a widely used nonsteroidal anti-inflammatory agent with hepatotoxic properties [26]. Several studies have shown that pretreatment of laboratory animals with ethanol and isopentanol, the predominant alcohols in alcoholic beverages, synergistically increases acetaminophen hepatotoxicity [27–29].
13. Ethanol is a very well-established hepatotoxin. A laboratory animal study has shown, however, that the hepatotoxicity of ethanol is magnified when ethanol ingestion is coupled with dietary iron overload. The authors of the study attribute the observed synergism to an increased pool of chelatable iron [30].

Table 30.3 Components of a Simulated Contaminated Groundwater Mixture That Induced Inflammatory Liver Lesions in Laboratory Animals

Acetone	Di(2-ethylhexyl) phthalate
Arachlor 1260 (PCB)	Ethyl benzene
Arsenic	Lead
Benzene	Mercury
Cadmium	Methylene chloride
Carbon tetrachloride	Nickel
Chlorobenzene	Phenol
Chloroform	Tetrachloroethylene
Chromium	Toluene
1,1-Dichloroethane	1,1,1-Trichloroethane
1,2-Dichloroethane	TCE
1,1-Dichloroethylene	Xylenes
1,2- <i>trans</i> -Dichloroethylene	

Source: Ref. [24].

30.4 Human Case Studies

The animal studies just described serve as models for understanding hepatotoxicity of chemical mixtures to humans. Many case studies reporting hepatotoxicity of chemical mixtures on humans have been reported in the literature. The following are illustrative of these studies, which demonstrate the unanticipated hepatotoxic effects of mixtures of lipophiles and hydrophiles. K_{ow} values are included for each chemical to demonstrate lipophilic or hydrophilic character.

1. Three previously healthy workers who worked in a plant that supplied chemicals for vitamin synthesis were hospitalized with liver injury following 2–4 months of exposure to a mixture of chemicals that included lipophilic and hydrophilic components:

Acrylonitrile	0.25
Carbon disulfide	1.94
Methanol	−0.77
Toluene	2.73

Concentrations of all species were below PELs and hepatotoxicity was not predicted. The authors of the study suggested that “liver injury was caused by the combined action of organic solvents.” Synergistic hepatotoxicity was suspected [31].

2. There are some 30,000 chemical waste dump sites in the United States. Many of these were established in the 1950s and 1960s when little was known about the need to contain the wastes buried in them. One such site is located in Hardeman County, Tennessee, where residents were exposed to leachate from that toxic waste dump in the drinking water drawn from nearby wells. The contaminants detected in these wells included the following chemicals:

Benzene	2.13
Carbon tetrachloride	2.83
Chlordene	5.44
Chlorobenzene	2.84
Chloroform	1.97
Hexachlorobutadiene	4.78
Hexachloroethane	4.14
Methylene chloride	1.25
Naphthalene	3.30
Tetrachloroethylene	3.40
Toluene	2.73
Xylenes	3.15

Those who were exposed to the contaminated drinking water sustained multiple liver effects compared with controls. The effects included increased elevation of alkaline phosphatase and serum glutamic oxaloacetic transaminase, as well as significantly lower albumin and total bilirubin levels [32].

3. Five workers at an industrial waste treatment plant in Ulsan, Korea, developed acute toxic hepatitis following the introduction of a new disposal process that resulted in their exposure to a large number of lipophilic and hydrophilic VOCs. The chemicals they were exposed to included:

1,4-Butanediol	-0.83
1-Butanol	0.88
2-Butoxyethanol	0.83
Butyl acetate	1.78
Cyclohexanone	0.81
Dimethyl acetamide	-0.77
DMF	-1.01
Pyridine	0.65
Tetrahydrofuran	0.46
Toluene	2.73
Xylene	3.15

Severe destruction of liver cells with bridging necrosis was observed in all five patients. None of the individual chemicals in the mixture had known toxicology that matched the clinical characteristics that were observed. The authors of the study suggested that “the various chemicals detected in the analysis underwent an interaction among themselves, which synergistically raised their toxicity compared with the original material” [33].

4. A study in Finland investigated 23 men with occupational liver injury. Eight of the subjects were interior and exterior house painters and the others were chemical industry workers. The painters were exposed daily to the following chemicals:

Acetone	-0.24
Benzene	2.13
1-Butanol	0.88
Butyl acetate	1.78
Butyl chloride	2.64
Ethanol	-0.32
Ethyl acetate	0.73
Ethylene glycol	-1.36
Methylene chloride	1.25
Toluene	2.73
Xylene	3.15

The compounds the chemical industry workers were exposed to included:

Acetone	-0.24
Benzene	2.13
Chloroform	1.97
Ethanol	-0.32
Toluene	2.73
Xylene	3.15

The affected workers all repeatedly had altered liver functions when examined in mandatory routine examinations compared with controls who had the same age distribution, dietary, and drinking habits as the subjects of this study. Industrial hygiene checks showed that all exposures in both groups of workers were below established limits for each of the chemicals, yet the low-level exposures to these mixtures of lipophiles and hydrophiles were hepatotoxic to individuals who were otherwise healthy and had no previous history of

liver disease. This study included controls who had the same age distribution, dietary, and drinking habits as the subjects of this study [34].

5. Fatty liver disease is generally attributed to alcohol, diabetes, or obesity. A study in Western Pennsylvania showed that it could also be attributed to exposure to chemical mixtures. A woman who used methylene chloride paint strippers developed fatty liver disease after using these strippers for more than 5 years [35]. Methylene chloride ($K_{ow} = 1.25$) paint strippers are mixtures of lipophilic and hydrophilic compounds, typically also containing methanol ($K_{ow} = -0.77$) and toluene ($K_{ow} = 2.73$).

This study also contained other examples of hepatotoxic effects of mixtures of lipophilic and hydrophilic chemicals, but the chemicals were described in generic form (e.g., glycol ethers and aerosol holding sprays) rather than as specific chemicals, precluding precise identifications of the chemicals involved.

6. Coke oven emissions are complex mixtures of hydrocarbons including benzene and polynuclear aromatic compounds; heavy metals including arsenic, beryllium, and cadmium; and other particulates and vapors. In a study of coking workers in Taiwan, it was found that liver function profiles were altered by exposures to coke oven emissions and that exposures to even low levels of these emissions were hepatotoxic. The authors of the study suggested that the adverse hepatotoxic effects are caused by a mixture of chemicals rather than by any one identifiable species [36].

30.5 Hepatic Cancer

The subject of chemically induced liver cancer will be addressed in Chapter 32.

30.6 Summary

The liver is essential in order to maintain life. Accordingly, xenobiotic attacks on it threaten life and well-being. Many chemicals are hepatotoxic, but mixtures of lipophilic and hydrophilic chemicals are liver toxins at exposure levels that are often far below those that are toxic for the single chemicals in those mixtures. Animal studies have demonstrated the hepatotoxic properties of such mixtures and case studies have confirmed these effects in humans.

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31 Kidneys

Chapter Outline

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31.1 Introduction

The kidneys are critical organs. They filter wastes produced by metabolism from the blood and excrete them with water as urine. They are also major organs in whole body homeostasis, with acid–base balance, electrolyte concentration regulation, blood volume control, and blood pressure regulation functions.

Because of their role as filtering organs, the kidneys are vulnerable to attack by a wide variety of xenobiotics, including halogenated hydrocarbons, aromatic hydrocarbons, ketones, glycol ethers, pesticides, heavy metals, and metabolites of other xenobiotics.

In addition to their filtration function, the kidneys are also metabolically active and carry out extensive oxidation, reduction, hydrolysis, and conjugation reactions, with enzymes' similar to those present in the liver and other extrarenal tissues involved in these metabolic reactions [1]. As has been previously noted, metabolites of xenobiotics are often more toxic than the parent compounds. As a result of the combination of the filtration and metabolic functions, the kidneys are targets for many toxic chemicals.

Large numbers of chemicals, including organic and inorganic, comprising a wide variety of functionalities are nephrotoxic. Many of the nephrotoxic effects are the result of OS and electron transfer parent compounds or metabolites giving rise to an ROS [2].

Many of the same chemicals that are hepatotoxic are also nephrotoxic. A partial list of renal toxins is contained in Table 31.1. This list is drawn from the Scorecard kidney toxicant lists, which contains references to original sources [3].

Table 31.1 Partial List of Renal Toxins

Acetanilide	Ethylene glycol
Acetic acid	Ethylene glycol monobutyl ether
Acetone	Ethylene oxide
Acetonitrile	Ethylenediamine
Aldrin	Formic acid
Arsenic	Furan
Biphenyl	Hydrazine
1,4-Butanediol	Lead
2-Butoxyethanol acetate	Mercury
Cadmium	<i>m</i> -Dichlorobenzene
Chlordane	Methanol
Chlorine	Methoxychlor
Chloroform	MEK
Chromium	Methyl <i>t</i> -butyl ketone
Cobalt	Mirex
Copper	Paraquat
Cyclohexanol	PCBs
DDT	PCP
Dibutyl phthalate	1-Pentanol
1,2-Dichloroethane	Phosphine
1,1-Dichloroethylene	Sodium metabisulfite
Dieldrin	TCDD
Diethylene glycol monoethyl ether	<i>tert</i> -Butanol
Dimethyl sulfate	Tetrachloroethylene
1,4-Dioxane	1,1,2,2-Tetrafluoroethylene
Dipropylene glycol monomethyl ether	Toluene
Endosulfan	Tributyl phosphate
Endrin	TCE
Epichlorohydrin	Xylenes
Ethyl acrylate	

31.2 Single Chemical Renal Toxins

As can be seen from Table 31.1 and associated references, many single chemicals are renal toxins. Several have been studied in detail. The following are illustrative examples:

1. Cadmium is a nephrotoxin found in food, tobacco, and in the general environment. A study of cadmium-induced nephrotoxic effects on Swedish women has shown that even low-level cadmium exposures in women who never smoked, significantly impacted renal tubular and glomerular function. The same study also found that cadmium potentiates diabetes-induced renal effects [4].
2. Thirteen different hydrocarbons, including aliphatics, aromatics, carbon tetrachloride, TCE, and other halogenated aliphatics, have been shown to cause glomerulonephritis (an inflammation of the kidney that can lead to the loss of kidney function and hypertension) in laboratory animals and humans [5] (and references contained therein).

3. Diethylene glycol was found to be responsible for an outbreak of acute renal failure in 109 Haitian children who had ingested a locally manufactured acetaminophen syrup. The glycerin contained in that syrup was found to be contaminated with 24% diethylene glycol [6].
4. The developing kidney is subject to attack by a number of environmental toxins. These include lead, cadmium, uranium, mercury, decalin, JP-5 jet fuel (a mixture of C_{12-15} straight and branched hydrocarbons), C_{10-11} isoparaffinic hydrocarbons, 2,2,4-trimethylpentane, D-limonene, diethylene glycol, and hexachlorocyclohexane [7].

Numerous other examples of single nephrotoxic agents exist. The discussion here focuses on the effects of mixtures, the subject for Section 31.3.

31.3 Nephrotoxic Chemical Mixtures

Given the almost constant exposure of humans to toxic chemicals (via air pollution, water pollution, or food contamination) and the filtration function of the kidneys, one could easily argue that the kidneys are almost constantly exposed to mixtures of toxic chemicals and that the uptake of additional xenobiotic chemicals creates new mixtures. As we have seen earlier, many single chemicals have been shown to be renal toxins. Whether the observed nephrotoxic effects of any of these chemicals are due to their interactions with endogenous or other exogenous chemicals is unknown. What is known is that exposures to some chemical mixtures are toxic to the kidneys of test animals and humans. Examples of studies demonstrating mixture effects are as follows:

1. JP-8 jet fuel is a complex mixture of primarily C_{8-20} aliphatic and aromatic hydrocarbons. Those living near airports and military aviation training sites are exposed to the volatile fraction of JP-8 by inhalation. Laboratory rats exposed via inhalation to JP-8 jet fuel vapors were shown to have protein alterations in their kidneys [8].
2. Laboratory animals were exposed to a mixture of chlorinated hydrocarbons at concentrations found in underground water near an electronic appliances factory in Taiwan. The mixture consisted of:
 - Chloroform
 - 1,1-Dichloroethane
 - 1,1-Dichloroethylene
 - 1,1,1-Trichloroethane
 - TCE
 - Tetrachloroethylene.

Though the exposures were to low levels of all chemicals, the exposed animals experienced multiple system effects, including increased kidney weights [9].

3. Chloroform, dichloroacetic acid, and TCA are disinfection by-products of water chlorination. In a study of laboratory rats it was shown that both dichloroacetic acid and TCA increase the renal toxicity of chloroform in test animals [10].
4. Carbon tetrachloride, which has been used in fire extinguishers as a fire suppressant, is a known renal toxin. In a study of people exposed to carbon tetrachloride vapors during fire-fighting activities, it was found that those individuals with histories of alcohol abuse experience greater nephrotoxic effects (including renal failure) than those who do not abuse alcohol. The authors of the study concluded that ethanol potentiates the nephrotoxic effects of carbon tetrachloride [11]. This is an example of a potentiated effect being

observed when exposure is to a mixture of a lipophile (carbon tetrachloride, $K_{ow} = 2.83$) and a hydrophile (ethanol, $K_{ow} = -0.32$).

5. The renal toxicity of carbon tetrachloride is also potentiated by isopropanol, as well as by ethanol. Workers in a chemical packaging plant were exposed to a mixture of vapors of carbon tetrachloride and isopropanol when the spacing between two packaging lines (one for each solvent) was small enough to create a mixed vapor atmosphere. Renal failure developed in 4 of the 14 workers so exposed. The authors of the study attributed the potentiating effect of isopropanol on carbon tetrachloride to acetone, a metabolite of isopropanol. They contrast this with the potentiation of ethanol on carbon tetrachloride, where it is the contaminant (ethanol) and not the metabolite that is the cause of the potentiation [12]. This is a further example of a potentiated effect being observed from a mixture of a lipophile (carbon tetrachloride, $K_{ow} = 2.83$) and a lipophile (acetone, $K_{ow} = -0.24$). Here, the lipophile interacts with the lipophile.
6. As has been discussed many times in this book, tobacco smoke contains some 4400 different toxic chemicals. Although several of the compounds contained in tobacco (including nicotine and cadmium) are renal toxins [13–15], not all nephrotoxic effects of tobacco smoke can be accounted for by a consideration of single chemicals alone. Renal function is impaired in cigarette smokers [16], and cigarette smoke aggravates glomerulosclerosis, tubulointerstitial, and vascular damage [17]. Inhaled tobacco smoke is also implicated in renal cell carcinoma [18], a subject that will be examined in Chapter 32.
7. Although both ethanol and tobacco smoke are renal toxins, a laboratory animal study demonstrated that the combination of the two produced nephrotoxic effects different from either one alone [19].

31.4 Summary

As filtering organs, the kidneys are almost constantly exposed to mixtures of toxic chemicals and their metabolites. Many single chemicals are nephrotoxic, but it is not always clear whether or not their toxicity is enhanced by interaction with endogenous or exogenous chemicals. Laboratory animal studies, however, have demonstrated and human observations have observed that the kidneys are subject to unanticipated toxic effects when living beings are exposed to mixtures of toxic chemicals.

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32 Cancer

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32.1 Introduction

Cancer is defined as “the uncontrolled growth and spread of cells that may affect almost any tissue of the body” [1]. As of 2007, 11 million people are diagnosed with cancer every year worldwide and it is estimated that this number will rise to 16 million new cases per year by the year 2020 [1].

WHO estimates that at least one-third of all cancers can be prevented by avoiding exposure to known carcinogens [1]. Others suggest that exposure to environmental carcinogens may account for a majority, perhaps as much as 75–80%, of all human cancers [2, 3].

It is currently believed by many, and supported here, that environmental influences coupled with genetic predispositions are responsible for the spectacular increase in diagnosed human cancers [4, 5]. It has been reported anecdotally by physicians who practice in preindustrial and traditional living societies (e.g., Canadian Inuits and Brazilian Indians) that cancer is rare in those societies [4].

There is much epidemiological evidence that the large numbers of cancers in those exposed to carcinogens are attributable to those exposures rather than to genetic factors. Cancer is more common in the following areas than in other areas with identical populations:

- Cities
- Farming locations
- Downwind of many industrial activities
- Near hazardous waste sites
- Pesticide use sites
- Hazardous waste incinerators [5].

Specific studies have definitively established the relationship between exposures and cancer. In one example of this phenomenon, all 15 workers in a chemical plant who were exposed to 2-naphthylamine during its distillation developed bladder cancer [6].

32.2 Cancer Incidence Rates

Cancer incidences, the number of new cases occurring annually, increased by 85% from 1950 to 2001. In 1950, one in four Americans would be diagnosed with cancer in his or her lifetime. By 2006, the odds of an American coming down with cancer in their lifetime increased to one in four in men and one in three in women. Incidence rate increases for some cancers, including lung, prostate, myeloma, thyroid, and non-Hodgkin's lymphoma, have risen dramatically in the past half century [5].

Genetic changes cannot account for this rapid increase in cancer incidence, for genes do not change that rapidly. This leads to the conclusion that environmental and occupational exposures to toxic chemicals are responsible for the increased incidence. The rapid increase in childhood cancer (a 22% increase from 1973 to 2000) provides highly convincing evidence for this conclusion. Relative to their

body weight, children drink 2.5 times more water, inhale 2 times more air, and eat 3 to 4 times more food than adults [7]. As seen in Chapter 6, children are also exposed to numerous chemicals in utero and from the consumption of breast milk. Epidemiological studies have linked elevated risks of childhood leukemia and brain cancers with parental and childhood exposure to solvents, pesticides, dioxins and PAHs [5]. Childhood cancer will be addressed in Chapter 36.

Cancer incidence rates are reported annually by the International Agency for Research on Cancer (IARC). In 2002, the latest year for which statistics are available, the five most prevalent cancers worldwide are:

Lung
Breast
Colon and rectum
Prostate.

For all these cancers, incidence rates are highest in the industrially developed areas of the world, where people are exposed to higher levels of carcinogenic chemicals. In each case, those living in areas with lower incidences for a particular cancer demonstrate increased rates when they migrate to areas with higher incidences [8], further demonstrating the cancer causative effects of environmental and occupational exposures to toxic chemicals.

32.3 Chemical Carcinogens

Several agencies have compiled lists of chemicals that are either established or suspected human carcinogens. The most widely used list is that of the IARC [9]. Other lists of chemical carcinogens include:

American Cancer Society [10]
NIOSH [11]
New Jersey Department of Health and Senior Services [12]
National Toxicology Program [13]
State of California Proposition 65 List [14]
Scorecard Recognized Carcinogens [15]
Scorecard Suspected Carcinogens [16]
U.S. EPA [17].

In addition, the U.S. Center for Disease Control has published a list of carcinogens in tobacco smoke [18].

Table 32.1 contains a list of human carcinogens compiled from the above-referenced sources and is divided into three groups as defined by IARC. The reader is referred to the literature for the complete lists of compounds [10–17].

Group 1	Proven human carcinogens
Group 2	Probable human carcinogens
Group 3	Possible human carcinogens

Table 32.1 Human Carcinogens

Chemical	K_{ow}
Group 1: Proven Human Carcinogens	
4-Aminobiphenyl	2.86
Arsenic and its compounds	0.68
Asbestos	NA
Benzene	2.13
Benzidine	1.34
BaP	6.13
Beryllium and its compounds	-0.57
Bis(chloromethyl)ether	0.57
1,4-Butanediol dimethanesulfonate	-0.52
Cadmium and its compounds	-0.07
Chloroambucil	4.44
Chloromethyl methyl ether	0.32
Chromium and its compounds	-3.54
Cobalt	0.23
Cyclophosphamide	0.63
Ethanol	-0.31
Ethylene oxide	-0.30
Formaldehyde	0.36
Mustard gas	2.41
2-Naphthylamine	2.28
Nickel and its compounds	-0.17
Propylene oxide	0.03
Polonium 210	NA
VC	1.62
Group 2A: Probable Human Carcinogens	
2-Acetylaminofluorene	3.12
Acrylamide	-0.67
<i>o</i> -Anisidine	1.18
Benzo(b)fluoranthene	5.78
Benzotrichloride	3.90
Benzyl chloride	2.30
1,3-Butadiene	1.99
Captafol	3.80
Chloramphenicol	1.14
Chloroprene	2.53
Chloroform	1.97
4-Chloro- <i>o</i> -toluidine	2.27
C.I. acid red 114	0.47
C.I. basic red 9 monohydrochloride	-0.21
C.I. direct blue 15	0.71
C.I. direct blue 218	-0.77
C.I. solvent yellow 14	5.51
Cisplatin	-2.19

(Continued)

Table 32.1 (Continued)

Chemical	K_{ow}
D&C orange no. 17	5.72
D&C red no. 8	1.75
D&C red no. 9	5.65
D&C red no. 19	1.95
3,3-Dichlorobenzidine	3.51
Diethyl sulfate	1.14
1,2-Dimethylhydrazine	-0.54
Dimethyl sulfate	0.16
3,3'-Dimethylmethoxybenzidine	1.81
Dimethylaminobenzene	4.58
1,4-Dioxane	-0.27
Epichlorohydrin	0.45
Ethyl carbamate	-0.15
Ethylene dibromide	1.96
<i>N</i> -Ethyl- <i>N</i> -nitrosourea	0.23
Lead and its compounds	-0.08
4,4'-Methylene bis(2-chloroaniline)	3.91
Methyl methanesulfonate	-0.66
<i>N</i> -Methyl- <i>N</i> -nitrosourea	-0.03
Nitrogen mustard	0.91
<i>N</i> -Nitrosodiethylamine	0.48
<i>N</i> -Nitrosodimethylamine	0.48
<i>N</i> -Nitroso- <i>N</i> -ethylurea	0.23
PCBs	6.29
Phenacetin	1.58
Procarbazine hydrochloride	-1.69
Propylene oxide	0.03
Silica dust	0.53
Styrene-7,8-oxide	1.61
Tetrachloroethylene	3.40
Thioacetamide	-0.26
Toluene-2,4-diisocyanate	3.74
<i>o</i> -Toluidine	1.32
TCE	2.42
1,2,3-Trichloropropane	2.27
Tris(2,3-dibromopropyl) phosphate	4.29
Vinyl bromide	1.57
Vinyl fluoride	1.19
Group 2B: Possible Human Carcinogens	
Acetaldehyde	-0.34
Acetamide	-1.26
Acrylonitrile	0.25
Aflatoxin M1	0.27
Alachlor	3.52

(Continued)

Table 32.1 (Continued)

Chemical	K_{ow}
<i>o</i> -Aminoazobenzene	4.29
<i>p</i> -Aminoazobenzene	3.19
Antimony trioxide	6.23
Atrazine	2.61
Azobenzene	3.82
Benz(a)anthracene	5.76
Bis(2-ethylhexyl) phthalate	7.60
Carbon black	NA
Carbon tetrachloride	2.83
Catechol	0.88
Chlordane	6.16
Chlordecone	5.41
<i>p</i> -Chloroaniline	1.83
Cobalt and its compounds	0.23
DDT	6.91
2,4-Diaminoanisoie	−0.31
4,4'-Diaminodiphenyl ether	1.36
2,4-Diaminotouene	0.14
Diazomethane	2.00
<i>p</i> -Dichlorobenzene	3.44
3,3'-Dichlorobenzidine	3.51
1,2-Dichloroethane	1.48
1,3-Dichloropropene	2.03
2,6-Dimethylaniline	1.84
DMF	−1.01
1,1-Dimethylhydrazine	−1.19
2,4-Dinitrotoluene	1.98
Ethyl acrylate	1.32
Ethyl benzene	3.15
Ethylene dibromide	1.96
Furan	1.34
Heptachlor	6.10
HCB	5.73
Hexachlorobutadiene	4.78
Hexachloroethane	4.14
Hexamethylphosphoramide	0.28
Hydrazine	−2.07
Hydrazine sulfate	−4.05
Isophorone	1.70
Methylene chloride	1.25
4,4'-Methylenedianiline	1.59
Michler's ketone	3.87
Naphthalene	3.30
Nickel and its compounds	−0.57

(Continued)

Table 32.1 (Continued)

Chemical	K_{ow}
2-Nitroanisole	1.73
Nitromethane	-0.35
<i>N</i> -Nitrosodimethylamine	-0.57
<i>N</i> -Nitrosopiperidine	0.36
PCP	5.12
Phenyl glycidyl ether	1.61
β -Propiolactone	-0.80
<i>n</i> -Propyl alcohol	0.25
Selenium sulfide	0.24
Styrene	2.95
TCDD	6.80
Tetrafluoroethylene	1.21
4,4'-Thiodianiline	2.18
Titanium dioxide	2.23
TDI	3.74
Vanadium pentoxide	2.97
Vinyl acetate	0.73
Vinylidene chloride	2.13

Included in the table are the K_{ow} values of the chemicals. As can be seen from the items on the list, many different types of chemicals are carcinogenic, including solvents, pesticides, heavy metals and PAHs. The K_{ow} values show that the list contains numerous lipophiles and hydrophiles. Items marked NA do not have K_{ow} values available.

The aforementioned lists also contain mixtures that are known or suspected carcinogens. These are listed in Table 32.2 by categories 1, 2A, and 2B as above.

All of the mixtures and exposure circumstances in Table 32.2 are associated with multiple individual chemical species that almost always contain both lipophiles and hydrophiles, and individual carcinogenic agents in these mixtures have not been designated. These are examples of exposures to mixtures inducing cancers that are not predicted from the individual components of the mixtures.

Cigarette smoke, the single most responsible cancer-causing agent known to man, contains numerous carcinogenic compounds [17]. These are listed in Table 32.3 by chemical type. The IARC carcinogenic groups, 1, 2A, or 2B, are also included.

32.4 Mechanisms of Carcinogenesis

It has been well established from epidemiological studies that environmental factors, including chemicals, radiation, and viruses, are causative of the majority of human cancers [2, 18]. The development of cancerous tumors in humans is widely believed

Table 32.2 Human Carcinogenic Mixtures

Group 1: Proven Human Carcinogens

Aflatoxins
Betel quid with tobacco
Betel quid without tobacco
Coal tar pitches
Coal tars
Household coal combustion emissions
Mineral oils
Soots
Tobacco, both smoked and smokeless
Wood dust
Smoking and tobacco smoke

Group 2A: Probable Human Carcinogens

Creosotes
Diesel engine exhaust
High-temperature frying emissions
Hot mate
Household wood combustion emissions
Insecticides from spraying and application
PCBs

Group 2B: Possible Human Carcinogens

Asphalt fumes
Bitumens
Gasoline engine exhaust
Fuel oil residuals
Gasoline
PBBs
Welding fumes

to almost always involve a multi-step process that includes an initiating step, a promoting step, and a propagation step [19, 20].

Agents that are initiators are capable of directly altering the genetic component of DNA. These agents are mutagens, interact with DNA and introduce faulty information into the DNA template. Single exposures to initiators may be sufficient to induce the carcinogenic process [21]. Examples of initiators include:

PAHs (e.g., BaP)
Nitrosamines (e.g., *N*-nitrosodimethylaniline)
Halogenated hydrocarbons (e.g., VC and ethylene dibromide)
Benzene
Cadmium
Formaldehyde.

Carcinogen-promoting agents are capable of altering the expression of genetic information of the cell as well as, in many cases, inhibiting apoptosis (programmed

Table 32.3 Carcinogens in Cigarette Smoke

Chemical	IARC Group
PAHs	
Benz(a)anthracene	2A
Benzo(b)fluoranthene	2B
Benzo(j)fluoranthene	2B
Benzo(k)fluoranthene	2B
BaP	2A
Dibenzo(a,h)anthracene	2A
Dibenzo(a,l,)pyrene	2B
Dibenzo(a,e)pyrene	2B
Indeno(1,2,3-cd)pyrene	2B
5-Methylchrysene	2B
Heterocyclic Compounds	
Quinoline	2B
Dibenz(a,h)acridine	2B
Dibenz(a,j)acridine	2B
Dibenzo(c,g)carbazole	2B
Benzo(b)furan	2B
Furan	2B
N-Nitrosamines	
N-Nitrosodimethylamine	2A
N-Nitrosoethylmethylamine	2B
N-Nitrosodiethylamine	2A
N-Nitrosodi-n-propylamine	2B
N-Nitrosodi-n-butylamine	2B
N-Nitrosopyrrolidine	2B
N-Nitrosopiperidine	2B
N-Nitrosodiethanolamine	2B
N-Nitrososornicotine	2B
4-(Methylnitrosoamino)-1-(3-pyridyl)-1-butanone	2B
Aromatic Amines	
2-Toluidine	2B
2,6-Dimethylaniline	2B
2-Naphthylamine	1
4-Aminobiphenyl	1
N-Heterocyclic Amines	
AaC	2B
IQ	2B
Trp-P-1	2B
Trp-P-2	2B
Glu-P-1	2B
Glu-P-2	2B
PhIP	2A
Aldehydes	
Acetaldehyde	2B
Formaldehyde	2A

(Continued)

Table 32.3 (Continued)

Chemical	IARC Group
Volatile Organic Hydrocarbons	
Benzene	1
1,3-Butadiene	2B
Isoprene	2B
Styrene	2B
Miscellaneous Organic Compounds	
Acetamide	2B
Acrylamide	2B
Acrylonitrile	2A
Caffeic acid	2B
Catechol	2B
1,1-Dimethylhydrazine	2B
DDE	2B
DDT	2B
Ethyl carbamate	2B
Ethylene oxide	2B
Methyleugenol	2B
Nitrobenzene	2B
Nitromethane	2B
2-Nitropropane	2B
Propylene oxide	1
VC	1
Inorganic Compounds	
Arsenic	1
Beryllium	1
Cadmium	1
Chromium (hexavalent)	1
Cobalt	2B
Hydrazine	2B
Lead	2B
Nickel	1
Polonium 210	1

cell death). Promoters do not chemically alter DNA, but have multiple biochemical effects. By affecting gene expression and enhancing the rate of replication of faulty information, they may lead to immortalization of the faulty genetic information. Promoters require multiple exposures and can act epigenetically, i.e., the promotion process can be interrupted and subsequently restarted [22–25]. Examples of promoters include:

- Asbestos
- Dinitrofluorobenzene
- PCBs
- Phenol

Di(2-ethylhexyl)phthalate
Phorbol esters (e.g., croton oil, phenobarbital).

Some agents are complete carcinogens, i.e., act as both initiators and promoters of carcinogenesis [26]. These include:

TCDD
Benzo(a)anthracene
Chrysene
Indeno(1,2,3-cd)pyrene
Alpha and gamma radiation.

Many xenobiotic chemicals are not by themselves carcinogenic, but require metabolism to the ultracarcinogens, which form DNA adducts. Examples of these include benzene and BaP, which are metabolized to their hydroquinones, the carcinogenic agents [18, 20, 27–29].

It is widely believed that OS is critical to carcinogenesis. OS theory states that bioactive agents (or their metabolites) that incorporate ET functionalities play crucial roles in carcinogenesis because of the following features common to most carcinogens [30–33]:

1. They bind to DNA by alkylation or complexation.
2. They show evidence of an ET entity being present in the parent compound or metabolite.
3. They form ROS by ET via the involvement of oxygen.
4. The ROS that are generated by these agents are in close proximity to DNA, giving rise to mutation via strand cleavage or DNA base oxidation.

A large number and variety of demonstrated carcinogens, including haloalkanes, quinones, benzenoid, and PAHs, aromatic nitro compounds, aromatic amines, metals, as well as other organic and inorganic compounds, have been shown to fit these criteria [30].

Asbestos is a known lung carcinogen. Mesothelioma is a cancer of the mesothelium, the membranes that cover the lungs and abdomen. This type of cancer is almost always caused by exposure to asbestos. A recently published study opines on the mechanism of asbestos-induced lung mesothelioma. It was found that when asbestos kills cells it acts via a process called programmed cell necrosis that leads to the release of a protein HMGB1. HMGB1 starts an inflammatory reaction that leads to the release of mutagens and tumor growth-promoting factors. These researchers found that those exposed to asbestos have elevated levels of HMGB1 [34]. It is estimated that 1 in 17 British carpenters born in the 1940s and who worked extensively in airborne asbestos-contaminated air environments will die of mesothelioma [35].

A complete discussion of cancer mechanisms is beyond the scope of this book. The reader is directed to Refs. [2, 18–33, 36] for a good introduction to the subject.

Whatever be the mechanism(s) for cancer development, one thing is clear: cancer is a largely environmentally caused disease. Three studies point this fact out dramatically.

In the first of these, a study of mummies worldwide has shown that they were virtually devoid of cancer. Of the hundreds examined, only two showed evidence of

cancer. None of the mummies examined in Egyptian and European museums had any evidence of cancer [36].

In the second study, of different Hispanic population groups, it was shown that members of those groups who live in the United States have a higher incidence of cancer than do their cohorts who live in their homelands. The authors of this study conclude that changes in environment and lifestyle are responsible for the increased cancer rates in those residing in the United States [37].

Thirdly, it is estimated that more than 70% of breast cancer cases are caused by environmental exposure or lifestyle and more than 200 chemicals are known to either alter or cause tumor formation in rodent breast tissue [38, 39].

32.5 Single Chemical Carcinogens

Many different cancers are caused by exposures single chemicals and many different compounds are known to induce some cancers. Some compounds are known to cause more than one cancer type. It is not the purpose of this book to exhaustively explore the hundreds of known single chemical carcinogens and the cancers they induce. The following, however, are some illustrative examples of these.

32.5.1 Cadmium

Cadmium is widely used in pigments, electroplating processes, and alkaline batteries. It is also a component of cigarette smoke. It has long been known to cause renal cancer in humans [40] and is also associated with cancer of the lung, pancreas, breast, prostate, and bladder [41].

32.5.2 Benzene

Benzene is a very widely used solvent and industrial chemical and a component of petroleum. It is a ubiquitous air pollutant and is formed as a decomposition product in fruit and soft drinks that are preserved with benzoates. Benzene is a known leukemogen and the one to which other leukemia-causing chemicals are compared [42–44]. Even low-level exposure to benzene has been shown to induce leukemia [44]. Benzene has also been associated with lung and nasopharynx cancers [45].

32.5.3 Arsenic

Arsenic is widely used in herbicide formulations and is widely distributed in drinking water. It is associated with cancers of the skin, lung, liver, kidney, and bladder [46, 47].

32.5.4 1,3-Butadiene

1,3-Butadiene is a widely used intermediate in the synthetic rubber industry. Exposure to it has been associated with the onset of leukemia [48].

32.5.5 Other Organic Solvents and Intermediates

Associations between human exposures to several organic solvents and intermediates and the onset of cancer have been made. These include:

- TCE—liver, non-Hodgkin's lymphoma, renal [45, 49]
- Tetrachloroethylene—esophagus, cervix [45]
- Carbon tetrachloride—lymphoma, leukemia [45]
- Styrene—leukemia [48]
- VC—liver [50]
- Bischloromethyl ether—lung [51].

32.5.6 Benzo[a]pyrene

BaP is a ubiquitous PAH that is emitted from cigarette smoke and the burning of petroleum products along with other PAHs. Epidemiological studies on humans and laboratory studies on animals have established BaP as a lung carcinogen [52]. Since human exposure to BaP is always accompanied by exposures to other chemicals, it cannot be absolutely stated that BaP acts alone as a carcinogen or is a part of cancer-causing mixtures.

32.5.7 Electromagnetic Radiation

As discussed in Chapter 16, a number of studies have linked the associations of electric and magnetic fields with increased risks of various carcinogenic end points, including leukemia, lymphoma, and brain cancer. Other studies, however, have refuted these associations. Illustrative of this dilemma is a Korean study that showed increased incidences of leukemia and brain cancer in those living in close proximity to some AM radio transmitters, but no such increased incidences in those living near other such transmitters [53]. At the time of this writing, the question of whether electromagnetic field exposure causes cancer remains an open one.

32.6 Occupational Exposures Known To Be Carcinogenic

Certain occupations are known to carry increased cancer risks with them. The IARC list of human carcinogens [9] names a number of these in each of its three categories.

Group 1: Proven Human Carcinogenic Exposures

- Aluminum production
- Auramine manufacture
- Boot and shoe manufacture and repair
- Chimney sweeping
- Coal gasification
- Coal tar distillation
- Coke production

- Furniture and cabinet making
- Hematite underground mining with radon exposure
- Involuntary smoking (exposure to secondhand smoke or ETS)
- Iron and steel founding
- Isopropyl alcohol manufacture via the strong acid process
- Magenta manufacture
- Painting occupationally
- Paving and roofing with coal tar pitch
- Rubber industry work
- Strong inorganic acid mists containing sulfuric acid
- Tobacco smoking and tobacco smoke.

Group 2A: Probable Human Carcinogenic Exposures

- Art glass
- Carbon electrode manufacture
- Cobalt metal with tungsten carbide fumes
- Hairdresser or barber
- Petroleum refining
- Sunlamp and sunbed use.

Group 2B: Possible Human Carcinogens

- Carpentry
- Dry-cleaning
- Printing
- Talc-based powder perineal use
- Textile manufacturing.

Virtually all of these occupations entail exposure to mixtures of chemicals with the carcinogenic agent(s) unidentified. Indeed, it is the mixtures, and not any particular components of them, that are cancer causing. Examples of carcinogenic mixtures of occupational chemicals are given in the next section.

32.7 Mixture Exposures Known To Be Carcinogenic—Many Component Mixtures

Many cancers are caused by exposures to mixtures of chemicals that are not individually carcinogenic. The hypothesis of this book is that these unanticipated effects are, in many instances, due to lipophilic species facilitating the absorption of hydrophilic species by transporting the lipophiles through the body's lipophilic barriers and thereby increasing exposure. Most of the carcinogens listed in Table 32.1 are hydrophilic compounds. For many of the lipophilic carcinogens, it is the hydrophilic metabolites that are the ultimate carcinogens. It is hypothesized here that in the case of mixtures, hydrophiles, that alone would not be absorbed in sufficient quantities to induce carcinogenesis, are absorbed in greater quantities due to the presence of lipophiles. This hypothesis is not inconsistent with the carcinogenic mechanisms described in Section 32.5, for no matter what the actual mechanism of carcinogenesis induction, cancer promotion is dose dependent and the absorption and delivery

of greater quantities of actual carcinogens to the critical sites is expected to increase cancer incidence.

The following are examples of carcinogenic mixtures described in the literature. Most of the mixtures are composed of lipophilic and hydrophilic components. K_{ow} values are given for single compounds where available. The designations (L) and (H) are used for lipophilic and hydrophilic mixtures, respectively, for which individual compounds are not discernible.

32.7.1 Metalworking Fluids

Metalworking fluids are widely used in machining and grinding. Four different classes of metalworking fluids are used:

- a. Straight oils that are naphthenic or paraffinic mineral oils (L) with additives that include sulfurized or chlorinated fats and corrosion inhibitors (H).
- b. Soluble oils that include mineral oils (L), as well as petroleum sulfonates, amine soaps, sodium naphthenates, triazines, chlorophenols, amines, and sodium nitrite (all H).
- c. Synthetic fluids including ethanolamines, nitrates, nitrites, phosphates, and borates (H), as well as alcohol and ester surfactants (L).
- d. Semisynthetic fluids that contain oils and ester lubricants (L) as well as glycols and polyols (H).

Workers using these fluids have been shown to have increased risks for cancers of the larynx, rectum, pancreas, skin, and bladder [51, 54, 55].

32.7.2 Lung Cancers Not Smoking Related

Lung cancer is most often associated with tobacco smoking (see Section 32.9). Nonsmokers, however, have also been found to have elevated incidences of lung cancer in some instances [56]. Three examples follow:

- a. Foundry workers who are exposed to complex mixtures of gases and fine particles that include airborne particulates (H) and organic binders (L) have an elevated risk for lung cancer. In vitro laboratory studies have demonstrated mutagenic activity for these fumes, including free-radical DNA damage [57].
- b. Lung cancer has also been attributed to diesel fume exposures [51]. Diesel fumes are composed of a complex mixture of lipophilic and hydrophilic species, including some that are individually carcinogenic (e.g., PAHs).
- c. Aluminum production workers are exposed to PAHs (L), asbestos, fluorides (H), sulfur dioxide (-2.20), and magnetic fields. A case-control Canadian study showed increased risks of lung cancer in aluminum production workers [58].

32.7.3 PAH Exposure and Cancer

Workers are environmentally exposed to PAHs in a number of industrial settings. Some of these are listed here. For each industry group, exposure to PAHs also

involves concurrent exposures to other chemicals. These are listed here for some of these occupational exposures along with the cancers associated with each [59]:

Chemical	Cancer
a. Aluminum Production	Lung
Asbestos (NA)	Bladder
Fluorides (H)	
Sulfur dioxide (−2.20)	
Magnetic fields (NA)	
b. Coal Gasification	Lung
Heavy metals (H)	Bladder
Silica (0.53)	Scrotum
Aromatic amines (L)	Skin
c. Coke Production	Lung
Heterocyclic aromatics (L)	Prostate
Substituted aromatics(L)	Kidney
d. Iron and Steel Foundry	Lung
Silica (0.53)	Stomach
Heavy metals (H)	Bladder
	Prostate
e. Chimney Sweeps	Scrotum
Carbon black (NA)	Lung
Arsenic (0.68)	Esophagus
Chromium (0.23)	Liver
Carbon monoxide (1.78)	Prostate
Sulfur dioxide (−2.20)	Kidney
Degreasing organic solvents (L and H)	Skin

Though all of these occupational groups are exposed to PAHs, each is exposed to distinctly different other chemicals as well. With the exception of lung cancer, the different cancers associated with each group point out the mixture effect. In all the groups, exposures are to lipophilic PAHs and to different combinations of other lipophiles and hydrophiles.

32.7.4 Painters

As pointed out in Chapter 12, painters are exposed to a multitude of lipophiles and hydrophiles including aliphatic and aromatic hydrocarbons, glycol ethers, alcohols, ketones, esters, residual monomers, and pigments. Painters have increased risks of lung, esophageal, stomach, and bladder cancer [51, 60]. A study of outdoor painters showed that occupational exposure to the commercially available paints they used resulted in increased cytogenic damage to buccal cells [61].

32.7.5 Pressmen

A study on deaths due to cancer among pressmen in the New York City metropolitan area revealed a significant increase in many cancers among this group [62]. These included cancers of:

- Buccal cavity and pharynx
- Esophagus
- Stomach
- Large intestine
- Rectum
- Liver
- Larynx
- Lung
- Bladder
- Kidney
- Brain and other CNS tissue
- Lymph.

Pressmen are exposed to ink mists, solvents, and cutting oils which contain numerous lipophiles and hydrophiles.

32.7.6 Rubber Industry Workers

Rubber industry workers are exposed to approximately 60 different accelerating, retarding, and antidegrading agents, as well as to a wide variety of solvent mixtures (including some with benzene) containing lipophilic and hydrophilic species. A review of the available epidemiological evidence revealed that these workers were found to have elevated risks for leukemia and cancers of the lung, bladder, and larynx [63]. The increased incidence of leukemia could not be entirely accounted for by the presence of benzene, since workers not exposed to benzene also had an elevated leukemia risk.

32.7.7 Oil Refinery and Petrochemical Workers

A study of Finnish oil refinery workers who were employed in a chemical products manufacturing plant for at least 5 years found significant excesses of kidney cancer, non-Hodgkin's lymphoma, and non-melanocytic skin cancer. These workers were exposed to a large number of lipophilic and hydrophilic chemicals [64]. These chemicals and their K_{ow} values are as follows:

Benzene	2.13
VC	1.62
Styrene	2.95
1,3-Butadiene	1.99
PAHs	4.50–6.50
Asbestos	NA
Nickel	−0.57
Chromium	0.23

A study of Australian petroleum industry workers showed significantly increased incidences of the following cancers:

Bladder
Prostate
Pleural mesothelioma
Leukemia
Multiple myeloma.

Though only asbestos was specifically named in the study, it can be reasonably anticipated that these workers were also exposed to a large number of aliphatic and aromatic hydrocarbons, PAHs, and heavy metals. The authors of the study attributed the mesotheliomas to asbestos exposure. The other cancers were not specifically attributed to causative chemicals [65].

A cohort mortality study of petrochemical workers in Texas found an increased incidence of malignant brain tumors in workers who worked in a plant that used numerous lipophilic and hydrophilic chemicals and manufactured 43 refined chemicals, four major classifications of resins, four industrial gases, and a mixture of straight chain hydrocarbons [66]. The cause of the observed cancers was not determined.

The findings of these three studies are of interest when considered together. Workers in all three studies were exposed to many of the same chemicals, yet different cancers were reported in all three. These studies point out the effects of subtly different chemical mixtures as cancer-causing agents and lend credence to the hypothesis that each specific mixture has a cancer-causing etiology of its own.

32.7.8 Hazardous Waste Sites and Water Pollution

Living in close proximity to hazardous waste sites and drinking water contaminated by leachates from these sites has been associated with numerous health problems, many of which have been discussed previously in this book. A study was carried out by the U.S. EPA on 593 waste sites in 339 counties in the United States with analytical evidence of contaminated drinking water being the sole source of water supply. In this study, significant associations were demonstrated for several cancers in both men and women [67]. These include:

Women	Men
Lung	Lung
Breast	Esophagus
Stomach	Stomach
Large intestine	Large intestine
Rectum	Rectum
	Bladder

Most of the cancers were the same in both genders, but notably only women had elevated incidences of breast cancer and only men had elevated incidences of cancers of the esophagus and bladder. No explanations were offered for these observed

differences. The study did not identify specific pollutants, but other studies have shown that typical contaminants leaching out of hazardous waste sites contain large numbers of lipophiles and hydrophiles, including organic solvents, pesticides, heavy metals, and other inorganics [68].

Surface waters are generally more polluted with runoff chemicals, including pesticides, fertilizers, and hazardous waste site leachates, than groundwater. A study of drinking water source and cancer rates that was carried out in Ohio showed that mortality rates for stomach and bladder cancers, as well as for all neoplasms, were higher for people who consumed surface water compared to those who consumed groundwater [69]. Similar risks for elevated cancer rates in those consuming polluted drinking water have been identified in studies carried out in China [70] and Finland [71].

Municipal solid waste sites release numerous chemicals into the air and water. In a study carried out in Montreal, Canada, it was found that men living near such a site were found to have excessive risk for developing cancers of the pancreas and liver, as well as non-Hodgkin's lymphoma [72].

32.7.9 Asphalt Fumes

Asphalt fumes are complex mixtures containing numerous organic compounds, PAHs and nitrogen-, sulfur- and oxygen-containing PAHs in vapor and aerosol form. Asphalt road pavers and highway maintenance workers are exposed to asphalt fumes by both inhalation and skin contact. These workers have been found to have high rates of lung cancer [9, 73, 74]. In a laboratory study it was found that when asphalt fume condensates were painted on the skin of test animals, DNA adducts were found in the lungs and other organs of these animals [73]. This suggests that both inhalation and dermal contact of asphalt fumes increase the risk for developing lung cancer.

32.7.10 Combined Action of Microwave Fields and Environmental Pollution

As discussed in Chapter 16, the question of whether or not thermal levels of microwave fields are toxic is a controversial one. One study, however, found that such microwaves act synergistically with chemical cancer promoters and lead to autonomous cell growth [75]. This effect has been demonstrated in vitro using the combination of cancer-promoting phorbol esters co-applied with nonionizing electromagnetic fields. The author of the study hypothesized that the mechanism of the combined radiation/chemical effect involves the disruption of normal intercellular communication through gap junctions.

32.7.11 Leather Tanning Industry

A Swedish study found that leather tannery workers had much higher incidences of prostate cancer than the general population [76]. The authors of the study compared the higher prostate cancer rates with those of farmers, who also had elevated

incidences of the disease, and attributed the increased rates in tannery workers to pesticide exposures, which they considered the causative carcinogens for farmers. The levels of pesticides to which tannery workers are exposed are orders of magnitude lower than those to which farmers are exposed. Leather tannery workers are, however, exposed to other chemicals, including lipophiles and hydrophiles [77–79]. These chemicals (and their K_{ow} values) include:

Toluene	2.73
Naphthalene	3.30
Amyl acetate	2.26
D-Limonene	4.57
Decanes and other aliphatic hydrocarbons	4.4–6.5
Trimethyl benzenes and other aromatic hydrocarbons	3.0–4.5
Diisobutyl ketone	2.56
2-Ethoxyethanol	–0.32
DMF	–1.01
Ethoxyethyl acetate	0.59
2-Butoxyethanol	0.83
Benzidine	1.34
<i>n</i> -Butanol	0.88
Acetone	–0.24

It is most probable that the causative agent for prostate cancer in leather tannery workers is a mixture of unknown composition. Working in the leather tanning industry is more commonly associated with increased prevalence of testicular cancer clusters [77–79]. This will be discussed in Chapter 33.

32.7.12 Pesticides

Many pesticides are classified by IARC as having sufficient or limited evidence for carcinogenicity [9]. These include herbicides, insecticides, fungicides, and other compounds. Table 32.4 contains a partial list of these.

Agricultural and industrial workers carry high risks for developing cancer following pesticide exposures [80]. Farming and other occupations that produce exposures to pesticides, including pesticide mixers, packagers, crop duster pilots, and others, are associated with increased cancer risks. Table 32.5 contains a partial list of occupational groups with exposures to pesticides [81].

Farmers and others occupationally exposed to pesticides have been found to be at greater risk for the following cancers:

- Brain
- Hodgkin's lymphoma
- Leukemia
- Lip
- Lung

Table 32.4 Partial List of Pesticides with Sufficient or Limited Evidence for Carcinogenicity

Herbicides	Fungicides
Atrazine	Captan
Diallate	Chlorothalonil
Nitrofen	Ethylene thiourea
Picloram	Formaldehyde
Trifluralin	HCB
Insecticides	PCP
Aldrin	Ziram
Arsenic	Others
Chlordane	Creosote
DDT	1,3-Dichloropropane
Dichlorvos	1,1-Dimethylhydrazine
Dieldrin	Ethylene dibromide
Methyl parathion	Methyl bromide
Mirex	
Toxaphene	

Table 32.5 Partial List of Occupational Groups with Pesticide Exposure

Farmers and farm workers	Wood preservation workers
Pesticide applicators	Pet groomers
Fumigation workers	Railway bed maintenance workers
Pesticide manufacturers	Highway crews
Crop duster pilots	Lawn care workers
Golf course workers	Nursery and greenhouse workers
Textile workers	

Melanoma
Multiple myeloma
Non-Hodgkin’s lymphoma
Prostate
Soft tissue sarcoma
Stomach
Testes.

The general public is exposed to pesticides via drinking water contamination, residuals in food, air pollution, and leaching from solid waste sites.

Pesticides are believed to be carcinogenic by multiple mechanisms including genotoxicity, tumor promotion, immunotoxicity, and hormonal action. This subject is addressed in some detail in an excellent review paper on pesticides and cancer [80].

Exposures to individual pesticides have been associated with some cancers. For example, phenoxyacetic acids, of which 2,4-D is the most widely used and researched, and chlorinated phenols carry risks of developing soft tissue sarcoma and non-Hodgkin’s lymphoma [82, 83]. It should be noted, however, that the authors of

one of the studies cited point out that though these associations are valid, phenoxy-acetic acid herbicides are usually used in combination with other pesticides and the associations are not to any single phenoxy herbicide alone [82]. The authors of the other study point out that conflicting results have been obtained in other studies, and that, "A further possibility is that phenoxy herbicides exposure could be carcinogenic only when occurring jointly with other exposures" [83].

In another example, California agricultural workers who were exposed to the pesticides mancozeb and toxaphene had increased incidences of leukemia compared with those not so exposed [84]. In this instance as well, the workers were exposed to other pesticides and toxic chemicals.

A more recent study (2006) also reported on the association between exposure by agricultural workers to 2,4-D and non-Hodgkin's lymphoma as well as leukemia and soft tissue sarcoma [85]. The authors conclude, however, that "It is not possible to distinguish whether these effects arise from 2,4-D itself, from breakdown products or dioxin contamination [which is common], or from a combination of ingredients."

The question of whether or not single pesticides are carcinogenic was addressed in a study on the herbicide atrazine, one of the most widely used herbicides in the world. In an *in vitro* study using human lymphocytes, atrazine alone was not genotoxic and did not induce apoptosis or necrosis. Atrazine, however, is not used as a pure active ingredient. Rather it is formulated with adjuvants to increase deliverability and activity. When tested in a commercial formulation, the atrazine-containing product increased DNA damage in the lymphocytes [86]. The adjuvant components of the commercial product were not identified and the material safety data sheet listed only atrazine as an active ingredient. This study points out the difficulty in making assessments of carcinogenicity of single pesticides.

32.7.13 Hematolymphopoietic Malignancies

Hematolymphopoietic malignancies (HLPs) include:

- Non-Hodgkin's lymphoma
- Hodgkin's lymphoma
- Leukemia
- Multiple myeloma.

Though it is known that some exposures lead to specific end points (e.g., benzene leads to leukemia [42–44, 136] and pesticides lead to non-Hodgkin's lymphoma [84]), the overall incidences of these malignancies have risen sharply in the past few decades. For example, non-Hodgkin's lymphoma incidence has doubled in the past 20 years [87, 88] and it is known that pesticide exposure is a risk factor for it [89]. Risk factors for leukemia and multiple myeloma include exposure to tobacco smoke as well as to emissions from petroleum refinery waste dumps [90]. Increased incidences of leukemia have been reported following exposures to mixed organic solvents [91] and gasoline [92]. Non-Hodgkin's lymphoma has also been linked to organic solvent exposure [93, 94]. Overall, the etiology of HLPs remains largely unknown. The known risk factors, including ionizing radiation, solvent exposure,

pesticide exposure, and immunosuppression, only account for a small percentage of the diagnosed cases worldwide [95].

Certain occupational exposures are associated with HLPs. These provide empirical evidence of associations between exposures and specific disease end points. Examples of these are as follows.

A case study in Sweden of 859 non-Hodgkin's lymphoma cases has shown an association between increased non-Hodgkin's lymphoma risk and industrial exposure to aliphatic hydrocarbons, aromatic hydrocarbons, mixed organic solvents, and gasoline as well as working as an automobile mechanic or painter [96].

Studies carried out in 12 different areas in Italy have demonstrated the following associations between occupation and HLPs [97, 98]:

Non-Hodgkin's lymphoma

- Cooks
- Waiters
- Bartenders
- Building maintenance workers
- Wood workers
- Textile workers
- Welders
- Metal workers
- Electricians
- Heavy machinery operators
- Dry cleaners
- Meat processors
- Hairdressers
- Farmers.

Hodgkin's lymphoma

- Textile workers
- Machinery fitters.

Leukemia

- Metal processors
- Material handlers
- Rubber workers
- Painters.

Multiple myeloma

- Hairdressers
- Metal processors
- Tailors
- Electrical workers
- Plumbers.

Other studies have also connected HLPs and hair treatment use [99], but HLPs from hair product use are not limited to salon workers. A study has shown that personal use of hair dyes by women resulted in increased incidences of non-Hodgkin's lymphoma and leukemia [100].

An Australian study has associated elevated risk of non-Hodgkin's lymphoma with occupational exposures to solvents, metals, organic dusts, wood dusts, and PCBs [101].

As discussed earlier, several studies have associated pesticide exposure with cancers. Non-Hodgkin's lymphoma has been associated with phenoxy herbicide exposure and specifically with exposure to 2,4-D [84, 102, 103].

Several studies have reported increased incidences of multiple myeloma that are related to occupational exposures. In a case-controlled study in Washington state, it was reported that work in the following occupations increased multiple myeloma risk [104]:

- Agricultural workers exposed to pesticides
- Fire fighters
- Petroleum manufacturing
- Coal products manufacturing.

Studies in Denmark among both men and women have shown elevated risks for multiple myeloma for those working in the following occupations [105, 106]:

- Synthetic yarn production
- Plastics manufacturing
- Plastic packaging
- Chemical production
- Metal fabricating
- Electrical plant work
- Retail sale of paint and wallpaper
- Orchard and plant nursery work.

The diversity of exposures for those in the occupations associated with HLPMS suggest that multiple mechanisms may be causative for these cancers. All the occupational exposures described above involve exposures to large numbers of chemicals, including lipophilic and hydrophilic species.

32.8 Mixture Exposures Known To Be Carcinogenic—Two-Component Mixtures

Several studies have demonstrated the induction of enhanced cancer-related responses from binary mixtures of xenobiotics. The following are illustrative of these effects. K_{ow} values are given for each chemical to demonstrate lipophilicity or hydrophilicity.

1. Bisphenol A (3.32) Nitrate (−0.79)

Bisphenol A (BPA), an endocrine-disrupting chemical, is commonly found in food packaging and can coatings. Nitrate is found in vegetables, fish, and in potable water as a pollutant. Bisphenol A alone did not exhibit mutagenicity toward *Salmonella typhimurium* strains TA 98 and TA 100 after incubation at pH 3.0 to simulate human stomach conditions. When nitrate was added to bisphenol A, however, the mixture showed strong mutagenic activity [107].

2. BaP (6.13) Sulfur dioxide (−2.20)

BaP and sulfur dioxide are ubiquitous air pollutants that result from petroleum fuel combustion, tobacco smoke, and other sources. BaP is carcinogenic, though sulfur dioxide

is not. Sulfur dioxide does, however, enhance the respiratory tract carcinogenesis of BaP when they are coadministered to laboratory animals [108, 109].

3. Styrene (2.95) Ethylene glycol (−0.136)

Workers occupationally exposed to mixtures of styrene and ethylene glycol in the paint and lacquer industry have been found to have significantly elevated blood plasma levels of malonaldehyde and 4-hydroxynonenal [110]. Styrene and ethylene glycol act synergistically to elevate the concentrations of these two aldehydes, which are implicated in carcinogenesis [111–113].

4. HCB (5.73) Iron (−0.77)

HCB is a liver carcinogen in rats, mice, and hamsters. Several studies have shown that iron, which is not a carcinogen, potentiates the hepatic carcinogenesis of HCB [114–117].

In all four of these enhanced effect binary mixture examples, one of the components was a lipophile and the other a hydrophile.

32.9 Tobacco and Cancer

Table 32.3 lists the known carcinogens in tobacco smoke. Added to the more than 4000 other chemical compounds contained in tobacco smoke, an almost infinite number of mixtures can be envisioned. This complexity makes it difficult to assign specific entities to individual cancers. Laboratory studies have, however, shown that some compounds, e.g., BaP, are carcinogenic to certain organs, in the case of BaP, the lung. Nitrosamines are also suspected of being carcinogenic to the lung and it is, at this time, not clear what compound or mixture of compounds is the true lung carcinogen [118]. It has been shown that nicotine promotes lung cancer [119] and not only individual genes, but entire networks of gene interactions are also influenced by cigarette smoking [120].

What is known is that smoking tobacco is associated with many cancers in humans [8, 118, 121–123]. These include the following cancers:

- Lung
- Oral cavity
- Laryngeal
- Nasopharyngeal
- Esophageal
- Oral
- Kidney
- Liver
- Pancreatic
- Bladder
- Stomach
- Colorectal
- Cervical
- Ovarian
- Breast
- Prostate
- Brain
- Leukemia.

Several components of tobacco smoke are known to be synergistically carcinogenic with each other. These include PAHs and catechol [124] and cigarette tar and nitric oxide [125]. Tobacco use, however, is always associated with exposures to other chemicals via environmental uptake, eating, and occupation. Several studies have demonstrated that the combination of tobacco smoking and exposure to other identifiable chemicals results in unanticipated and enhanced carcinogenic effects. Examples of these follow.

32.9.1 Tobacco and Asbestos

Both tobacco smoke and asbestos are associated with elevated risks for the development of lung cancer. Asbestos workers who smoke, however, are 8 times as likely to develop lung cancer than non-asbestos-exposed smokers and have a 92-fold greater risk for lung cancer than nonsmoking, non-asbestos workers [126]. Asbestos also enhances the mutagenesis of BaP, a component of cigarette smoke. Studies with laboratory animals have suggested that the asbestos enhancement is due to its fibers' adsorption of BaP and the physical effect of the fibers on cell membrane structure [127].

32.9.2 Tobacco and Arsenic

In a study of 228 Swedish copper smelter workers, it was found that the age standardized rate ratio for lung cancer death was 3.0 for arsenic-exposed nonsmokers, 4.9 for smokers not occupationally exposed to arsenic, and 14.6 for arsenic-exposed smokers, demonstrating a multiplicative effect of the combined exposure [128].

32.9.3 Tobacco and Alcohol

Smokers who consume alcohol have enhanced rates of upper alimentary canal cancers [129]. Although the mechanism for alcohol-enhanced carcinogenesis is not well understood, it is thought that acetaldehyde, the first metabolite of ethanol, is the cancer-causing agent [130]. Tobacco contributes to increased acetaldehyde formation by altering the oral bacteria flora [131].

32.9.4 Tobacco and Radon

Smoking and exposure to radon have a synergistic multiplicative effect on lung cancer incidence [132]. This effect has been observed in instances of household radon/smoking combinations [133] as well as in industrial dual exposures, most notably in mining populations [134]. No well-understood mechanism to account for this effect exists at this time.

32.10 Summary and Outlook

Cancer prevalences worldwide continue to grow at alarming rates that cannot be accounted for solely by genetic predisposition. Epidemiological and laboratory studies

have definitively connected some cancers to occupational and environmental chemicals. In most instances, however, the causative agents remain unknown. This uncertainty is believed to be due to the effects of mixtures whose compositions are variable and constantly changing with environmental conditions. The available studies demonstrate, however, that most carcinogenic mixtures contain both lipophilic and hydrophilic components. In many instances, mixtures of lipophiles and hydrophiles that are not individually carcinogenic induce cancers when people are exposed to these mixtures.

Remarkable progress has been made in the diagnosis and treatment of cancer. Despite this progress, cancer-related deaths worldwide continue to increase regularly and the increase is directly related to ever-increasing environmental contamination by toxic chemicals. An example of the ever-increasing prevalence of cancer is breast cancer, the most frequent cancer in women. Despite thousands of studies, the etiology of breast cancer remains poorly understood [135].

Identification and elimination of the carcinogenic agents from the environment is crucial if the war on cancer is to be won. Treatment alone cannot bring success.

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33 Cancer Clusters

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33.1 Introduction

A cancer cluster is an outbreak of a particular cancer or cancers in a group of individuals in greater than expected numbers following a common exposure by that group to a causative agent or agents [1]. In investigating cancer clusters, researchers are able to study the effects of chemical exposures on cancer epidemiology with other variables removed.

Many cancer clusters have been associated with exposures to individual chemicals. A number of these, however, have followed exposures to mixtures of chemicals. Those who have investigated these mixture exposure clusters have focused their attention on finding the individual components of the mixtures that were the causative agents.

It is hypothesized here that the mixtures, and not single components of these mixtures, are the causative agents for many cancer clusters. Several previously unexplained cancer clusters all have common elements:

1. All can be attributed to exposures to chemical mixtures that contain at least one lipophile and at least one hydrophile.

2. The combinations of lipophiles and hydrophiles produce cancers in unexpected organs not known to be targets for the individual components of the mixtures.
3. The cancers induced are not associated with exposure to any of the individual chemicals that make up the mixtures.
4. The cancer clusters may be in the form of single cancer per cluster or of specific multiple cancers per cluster.

33.2 Mixture-Induced Cancer Clusters

The following are examples of cancer clusters reported in the literature that are unexpected, i.e., that cannot be attributed to any single causative agent. In all cases, the cancer clusters followed exposures to mixtures of lipophiles and hydrophiles. K_{ow} values are given for each chemical to demonstrate lipophilic or hydrophilic character.

33.2.1 Cluster 1: Childhood Leukemia

Woburn, Massachusetts was the location of a cluster of childhood leukemia from 1969 to 1979 [2–4]. The cluster was associated with contaminated municipal well drinking water that contained the following chemicals:

Tetrachloroethylene	3.40
1,1,2-Trichloro-1,2,2-trifluoroethane	3.09
1,1,1-Trichloroethane	2.49
TCE	2.42
<i>trans</i> -1,2-Dichloroethylene	2.09
Chloroform	1.97
PAHs	4.50–6.50
Arsenic	0.68
Chromium	0.23

Though arsenic and chromium have been associated with some cancers, none of these chemicals individually are known to be causative for leukemia.

33.2.2 Cluster 2: Prostate Cancer

A cluster of prostate cancer deaths was reported among a group of oil refinery workers. These workers used a mixture of chemicals to remove wax from crude oil in a lubricating oil manufacturing process [5]. The chemicals used included:

Benzene	2.13
Toluene	2.73
MEK	0.29

Benzene is a known leukemogen. Leukemia, however, was not reported. None of these chemicals are known to cause prostate cancer.

33.2.3 Clusters 3–6: Testicular Cancer

Three different testicular cancer clusters have been reported among leather tannery workers [6–8]. These workers are exposed to a wide range of lipophilic and hydrophilic chemicals that include:

Toluene	2.73
Naphthalene	3.30
Amyl acetate	2.26
D-Limonene	4.57
Decanes and other aliphatic hydrocarbons	4.40–6.50
Trimethylbenzenes and other aromatic hydrocarbons	3.00–4.50
2-Ethoxyethanol	−0.32
DMF	−1.01
2-Ethoxyethylacetate	0.59
2-Butoxyethanol	0.83
Diisobutyl ketone	2.56
Benzidine	1.34
<i>n</i> -Butanol	0.88

The chemicals used also included other aldehydes, alcohols, esters, and nitrosamines.

A testicular cancer cluster was also reported among military aircraft repair personnel [9]. The chemicals these workers were exposed to included:

1,1,2-Trichloro-1,2,2-trifluoroethane	3.09
1,1,1-Trichloroethane	2.49
DMF	−1.01
MEK	0.29

Because DMF was used in the tannery and aircraft repair workplaces, it was hypothesized that it was the causative agent for the testicular cancer outbreaks. DMF alone, however, is not known to cause testicular cancer and the authors of all four studies concluded that DMF was not the sole carcinogen but that the large numbers of other chemicals to which these workers were exposed make it difficult to establish DMF as the causative agent.

33.2.4 Cluster 7: Brain Cancer Cluster—Electronic Workers

A brain cancer cluster was found at an electronics components manufacturing plant [10]. The chemicals used in the plant included:

Beryllium metal	−0.57
TCE	2.42

Cutting fluids and balancing fluids, containing amines, halogenated aromatic hydrocarbons, and chlorofluorocarbons with K_{ow} values ranging from 1.50 to 3.50, were also used in that plant. None of the individual chemicals these workers were exposed to are known to cause brain cancer.

33.2.5 Cluster 8: Brain Cancer Cluster—Petrochemical Workers

A brain cancer cluster was documented among petrochemical workers [11]. The raw materials and chemicals manufactured in the plant included a broad range of lipophilic and hydrophilic compounds, among which were:

Ethylene oxide	−0.30
Ethylene glycol	−1.36
Isopropanol	0.05
Acetaldehyde	−0.34
VC	1.63
Butadiene	1.99
Benzene	2.13
Toluene	2.73
Styrene	2.95
Xylene	3.15

None of these chemicals is individually known to cause brain cancer in offspring only, and no unusual cancer prevalences were identified for the exposed.

33.2.6 Cluster 9: Brain Cancers in Offspring of Electronic Workers

A unique cancer cluster was reported in which children of parents (both mothers and fathers) who worked at the same electronics manufacturing plant developed intracranial neoplasms [12]. Parents were exposed to some 30 different chemical classes containing more than 100 different compounds. These compounds included:

TCE	2.42
Toluene	2.73
Amyl acetate	2.26
Methylene chloride	1.25
Carbon monoxide	1.78
Nitric acid	0.21
Hydrofluoric acid	0.23
Sulfur dioxide	−2.20

Despite the large number of lipophiles and hydrophiles to which these workers were exposed, only one cancer type was reported in workers.

The three cancer clusters just discussed are interesting to analyze. Two different sets of chemical mixtures (in electronics workers and petrochemical workers) induced brain cancers in those exposed, while in one instance (the second electronics

worker group) only the children of those exposed developed brain cancer. These studies show that different mixtures of chemicals can induce the same cancer types and that different mechanisms are at work in the development of the same cancer type. In all three clusters, none of the individual chemicals that the workers were exposed to are known to be causative for brain cancer.

33.2.7 Cluster 10: Kidney Cancer Cluster

A cluster of kidney cancers developed in workers at a printed paperboard box manufacturing plant [13]. These workers were exposed to a mixture of the following chemicals, as well as to several ink pigment waxes, additives, and adhesives. These are as follows:

TCE	2.42
Methylene chloride	1.25
Formaldehyde	0.35

None of the chemicals to which these workers were exposed is known to cause kidney cancer. The results of this study are interesting when compared to those reported for commercial pressmen who worked with many of the same chemicals [14]. The commercial pressmen had increased numbers of all cancers, while the printed paperboard box workers had a cluster of kidney cancers only, with no other cancer increases observed. This comparison points out the unique nature of the mixture to which the printed paperboard box workers were exposed, which triggered kidney cancer only, and in large numbers.

33.2.8 Cluster 11: Colorectal Cancer Cluster

A colorectal cancer cluster was reported in a polypropylene manufacturing plant [15]. The chemicals used included:

Methanol	0.77
Xylene	3.15
<i>n</i> -Pentane	3.39
BHT	5.10

A number of surfactants and plasticizers with K_{ow} values ranging from 1.00 to 2.50 were also in use in that plant. None of the chemicals that were in use were individually known to cause colorectal cancers.

33.2.9 Cluster 12: Multiple Cancer Cluster

Multiple cancers were reported among workers with exposures to rocket-engine test stands [16]. Workers in the area were exposed to:

Monomethyl hydrazine	– 1.05
Kerosene fuels	2.50–6.50
TCE	2.42

The workers were also exposed to asbestos, radiation, and other unspecified chemicals. Positive associations were observed between the exposures and rates of death from lung, lymphopoietic, bladder, and kidney cancers. Kerosene fuels, which contain PAHs and asbestos, are associated with lung cancer, but not with the other cancers. Methyl hydrazine is not a known human carcinogen. Similar results were reported for carcinogenic effects of lipophilic PAHs in combination with hydrophilic chemicals for aluminum workers, coal gasification workers, and chimney sweeps [17].

33.2.10 Cluster 13: Lung Cancer Cluster

A lung cancer cluster was identified in steel mill workers who worked in the melt shop of an electric steelmaking operation [18]. That mill cast carbon and specialty steels from scrap metals. The raw materials for the plant included automobile industry scrap, construction materials, and containers which were coated with oil-based and other organic materials. Flue dust analysis revealed the following hydrophilic compounds:

- Aluminum oxide
- Calcium oxide
- Chloride
- Chromium (III) oxide
- Copper (II) oxide
- Magnesium oxide
- Manganese oxide
- Manganese dioxide
- Sodium oxide
- Nickel (II) oxide
- Phosphorus pentoxide
- Lead oxide
- Stannous oxide
- Titanium dioxide
- Vanadium pentoxide
- Zirconium oxide.

In addition, carbon black, sulfur, and numerous lipophilic organic materials were identified. Environmental assessment was unable to identify any single lung carcinogen. The authors of the study point out that lung cancer has not been previously associated with working in an electric arc steel mill. The inorganic compounds identified are commonly found in steel mills. It is thought here that the organic impurities contained in the steel scrap combined with the inorganic compounds formed a mixture that is carcinogenic to the lung.

33.2.11 Cluster 14: Childhood Leukemia

Sixteen children who lived in Fallon, Churchill County, Nevada at the time of or before becoming ill were diagnosed with leukemia between 1997 and 2002. The

expected rate for the population of the county is about one in every 5 years. Toxic exposures came from several sources:

- a. The drinking water was found to contain elevated levels of uranium, arsenic, and radon.
- b. Surrounding fields were regularly sprayed with pesticides.
- c. A pipeline carrying millions of gallons of JP-8 fuel to a nearby naval base runs through the center of town and large numbers of flights have resulted in the airborne release of fuel combustion products and residues [19–23].

The chemicals that the residents were exposed to included:

Arsenic	0.68
Uranium	0.23
Radon	1.53
Carbon monoxide	1.78
Benzene	2.13
Toluene	2.73
Xylene	3.15
PAHs	4.50–6.50
Aliphatic hydrocarbons	3.50–5.00
Formaldehyde	0.35
Oxides of nitrogen	–0.60 to 0.10
1,1,1-Trichloroethane	2.49
1,4-Dichlorobenzene	3.44
Carbon tetrachloride	2.83
Ethyl benzene	3.15
Styrene	2.95
TCE	2.42
Tetrachloroethylene	3.40
Chlorpyrifos	4.96
Diethyldithiophosphate	2.24
2,4-Dichlorophenol	3.06
2,4,5-Trichlorophenol	3.72
2-Naphthol	2.70
DDE	6.51

Though benzene was found in the air samples taken, its level was far below that associated with being causative for leukemia. With the exception of naturally occurring arsenic, none of the other chemicals the children were exposed to was considered to be above acceptable levels and none was causative for leukemia.

33.2.12 Cluster 15: Multiple Cancer Clusters

Naval divers in Israel train in the Kishon River. Pollution in the Kishon River ranks among the highest in the world, reaching levels close to those in the Rhine, Alba, and Po rivers. Divers who have trained in these waters form a cancer cluster of

multiple cancers that are not only far in excess of cancers in the general population, but also have very short induction periods [24]. The cancers found in the divers include:

- Hematolymphopoietic
- CNS
- Gastrointestinal
- Skin.

Exposures to pollutants come via dermal contact, inhalation of vapors, and swallowing of river water.

The sources of pollution in the Kishon River are industrial effluents, dredging of sediments, fertilizer runoff, and dumping of waste. The contaminants include numerous lipophilic and hydrophilic compounds, among which are:

- PAHs
- Benzene
- Toluene
- Xylene
- Styrene
- Long-chain branched hydrocarbons
- Phenols
- Alcohols
- Chlorinated alkylbenzenes
- TCE
- Trichlorophenol
- Cresols
- Cycloalkanes
- Aldehydes
- Ketones
- Brominated and chlorinated aromatic organic compounds
- Di-(2-ethylhexyl)phthalate
- Diphenyl
- Hexachlorocyclohexanes
- Methylene chloride
- Carboxylic acids
- Inorganic acids
- Fertilizers and their by-products
- Nitrogen by-products
- VC
- Heavy metal salts
- Uncharacterized dusts
- Powdered cement.

No single agent has been identified as causative for any of these cancers.

33.2.13 Cluster 16: Toxic Waste Disposal Site-Related Clusters

Toxic waste sites emit a multitude of lipophilic and hydrophilic compounds to the water and air around them. Health effects from toxic waste site leachates have been

discussed previously in this book. The emissions from these sites are also causative for cancer clusters. Identified toxic waste disposal site-related cancer clusters include 13 gastrointestinal cancer clusters in New Jersey municipalities [25]; clusters of primary gastrointestinal cancer in Delaware, Maryland, Pennsylvania, Virginia, and West Virginia [26]; and brain and CNS cancers in children under the age of 5 in Toms River, Dover Township, New Jersey, located near two superfund sites [27]. In all these clusters, no single causative agents were identified.

33.3 Summary

Most cancer cluster studies have focused on identifying single-compound causative agents. Most of these clusters, however, result from exposures to mixtures of chemicals. Analysis of the cancer clusters reported in the literature, many of which are described earlier, reveals that all of the unexplained clusters ensue following exposures to chemical mixtures that contain at least one lipophilic and one hydrophilic chemical. These mixtures act as unique entities to produce specific cancer clusters whose locations are not predicted by the known toxicology of the single compounds that comprise the mixtures.

Many cancer clusters remain unexplained. The cluster of breast cancer in Marin County, California is an example. No chemicals (with the possible exception of ethanol) have been identified as causative agents and lifestyle choices (diet, drinking of ethanol, age of first pregnancy, and so on) have been suggested as responsible [28, 29]. Variations in cancer rates in different parts of the county and the finding that women living near toxic waste sites have increased incidences of breast cancer [30], however, suggest that the true causative agents remain to be identified and that chemical exposures cannot be eliminated.

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34 Nanotoxicology

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34.1 Introduction

Nanoparticles (NPs) are those with diameters of less than 100 nm (1 nm = one billionth of a meter) in one dimension or less than 1000 nm for aggregates and agglomerates. NPs are 100–10,000 times smaller than mammalian cells. Nanotoxicology addresses the toxic effects of NPs on living systems [1].

Humans have been exposed to NPs throughout their evolution via inhalation of ultrafine particles produced by fires, volcanic action, and other natural phenomena. Human exposure, however, has been dramatically increased in the past 20 years as a result of the rapidly developing field of nanotechnology, which has produced large numbers of synthetic nanosized particles. These synthetic particles are readily absorbed by humans via inhalation, ingestion, dermal uptake, and injection. Some of these exposures are deliberate as parts of drug-delivery systems [2]. This chapter reviews the types of NPs that people are exposed to, the sources of these particles, and their toxic effects on humans. The toxicology of NP exposure is a part of science in its infancy. The reader is referred to the literature for a more thorough introduction to nanotoxicology [1, 2].

34.2 Nanoparticles

NPs are classified as one of two types—natural (also referred to as environmental) or anthropogenic (also referred to as man-made or manufactured). Anthropogenic NPs are further classified as unintentional or intentional NPs.

34.2.1 *Natural NPs*

Natural NPs include carbon black, hydrocarbons, sulfur, heavy metals, inorganics, and biologicals. Sources for these include:

- Forest fires
- Volcanoes
- Sea spray
- Airborne soil dust particles
- Viruses.

34.2.2 *Anthropogenic: Unintentional NPs*

Unintentional anthropogenic NPs include carbon black, hydrocarbons, heavy metals, noble metals, inorganic compounds, synthetic organic compounds, hydrocarbons, and asbestos. Sources for these include:

- Electrical power plants
- Internal combustion engines
- Jet engines
- Smelting fumes
- Welding fumes
- Polymer fumes
- Cooking fumes
- Catalysts
- Friction devices such as vehicle brakes and electric motors
- Tobacco smoke.

34.2.3 *Anthropogenic: Intentional NPs*

Intentional anthropogenic NPs include metals, metal oxides, and CNTs. Sources for these include:

- Semiconductors
- Cosmetics
- Medical applications, including drug-delivery systems
- Optical displays
- Electronic applications
- Fumed silica.

34.3 NP Uptake

NPs are absorbed into the bodies of humans via inhalation, ingestion, dermal uptake, and injection.

34.3.1 *Inhalation*

Inhaled NP uptake occurs in all three parts of the respiratory tract: the nasopharyngeal region, the tracheobronchial region, and the alveolar region [2]. Absorption in all three regions produces inflammation and results in footprints that are unique to the specific nanochemicals that are absorbed. Accordingly, NPs cannot be considered as a single hazard and each specific NP must be tested for its toxic effects. Some NPs have been found to trigger asthmatic-type reactions while others have been shown to worsen lung injury [3].

34.3.2 *Ingestion*

NPs can be ingested directly if present in food or water that is consumed, or they can be ingested by swallowing NP-containing mucus that is cleared from the lungs. Following ingestion, NPs can pass into the blood and be transported to other body organs, including the liver, spleen, kidneys, bone marrow, brain, and other nerve tissue [2, 4].

34.3.3 *Dermal Uptake*

NPs can be absorbed through the skin and can also enter the body through broken skin [2, 5]. Once absorbed, NPs translocate to lymph nodes and ultimately to the bloodstream from where they distribute throughout the body.

34.4 Mechanisms of Toxic Effects of NPs: OS

NPs are generally believed to exert toxic effects via a number of mechanisms, all of which are related to OS [6, 7]. The extent of the effects noted has been well correlated with Brunauer, Emmett, and Teller (BET) [8] surface areas of the NPs in a number of studies [9, 10]. BET surface areas are widely used to evaluate catalytic activity in promoting chemical reactions and it is well known that the quantity of surface and not the mass of a heterogeneous catalyst is what determines the degree of chemical reaction [11]. It is currently believed that insoluble NPs act in an analogous manner.

It is beyond the scope of this book to thoroughly explore the mechanisms by which NPs produce toxic effects. The reader is referred to Refs. [6–10] for a good introduction to this subject.

34.5 Case Studies: NP Mixtures

As of this writing in 2011, few studies have been carried out on the toxic effects of mixtures of different species of NPs or of single NP species on which liquids and gases are absorbed. Very few of these studies have addressed human exposures to such mixtures. Studies that have been carried out, however, demonstrate that single species of NPs produce unanticipated toxic end points [25–33]. The few studies that address mixture effects have also produced unpredicted toxic effects. The following studies are representative of those that have been carried out to date.

34.5.1 Carbon Nanotubes

CNTs can have single-wall (SWCNTs) or multi-wall (MWCNTs) structures. They are manufactured by electric arc discharge, laser ablation, and chemical vapor deposition processes. Catalytic metals are used to form SWCNTs, resulting in the likelihood that metal residues are present in these materials. Studies in which dusts containing SWCNTs and MWCNTs were administered intratrachially or intrapharyngeally to rodents have shown that both CNTs types, regardless of the types or quantities of metals contained, impact the lungs. These impacts include inflammation, epithelioid granulomas, fibrosis, alveolar wall thickening, biochemical changes, decreased bacterial clearance, respiratory deficiencies, and toxicological effects in the lungs [12–15]. One study compared the effects of SWCNTs with those induced by ultrafine carbon black and fine crystalline silica particles. Equal doses of these did not induce the granulomas and alveolar wall thickening that SWCNTs did. The carbon and silica also caused significantly weaker pulmonary inflammation and structural damage to the lungs than the SWCNTs [14].

It should be noted that MWCNTs and other carbonaceous NP aggregates have been found in methane, propane, and natural gas flames of stoves and furnaces typically used for residential and commercial cooking and heating [13]. This finding implies that many people routinely inhale MWCNTs and this suggests further research into the toxic effects on those who are so exposed.

34.5.2 Cardiovascular Disease

Inhaled CNTs are rapidly absorbed and passed into the blood of humans. In a study involving human volunteers, Technigas (an aerosol of radioactive technetium-labeled carbon NPs in the range of 5–10 nm) was shown to rapidly diffuse into the human blood. The authors concluded that carbonaceous air pollution could impact cardiovascular morbidity and mortality [16].

Two other studies have concluded that inhalation of nanosized particulates is associated with increased rates of myocardial infarction (MI). In the first study, carried out in southern Germany, the authors concluded that transient exposure to traffic (which contaminates air with nanosized particulates) may increase the risk of MI in susceptible individuals [17].

A second study, carried out in the Boston, Massachusetts area, surveyed 772 patients with MI and compared incidences of MI with airborne-fine-particle content. The study concluded that exposure to nanosized particulates may elevate the risk of MIs within a few hours and 1 day after exposure [18].

34.5.3 Respiratory Disease

Several studies have demonstrated adverse respiratory effects on humans following inhalation of ultrafine particles associated with air pollution and diesel fumes [19–24]. The studies cited clearly demonstrate that nanoparticulates inhaled from ambient air are toxic to the respiratory system. In these studies, however, the chemical nature of the NPs was only generally described. A study of lung disease following inhalation of particulates by responders to the World Trade Center (WTC) disaster on September 11, 2001 provides valuable information regarding pulmonary responses to identified inhaled nanoparticulate mixtures [24]. These results are described as follows.

On September 11, 2001, lower Manhattan and parts of Brooklyn, New York, were engulfed by a cloud of dense smoke that was generated when the twin towers of the WTC collapsed. Seven previously healthy responders who were exposed to WTC dust on either September 11 or 12 developed moderate to severe respiratory impairment. Lung biopsies of the seven individuals revealed the presence of the following NP-sized materials:

- Aluminum silicate
- Magnesium silicate
- Chrysotile asbestos
- Calcium phosphate
- Silica
- CNTs.

It should be noted that minerologic analysis showed that the lung tissues of six of the seven patients had different compositions of particulate matter and that no particulate matter was found in the lungs of one of the individuals. It should also be noted that the analyses carried out did not consider soluble inorganic salts and alkalis, and VOCs, that could have affected these people.

The symptoms reported by the seven patients included the following:

- Dyspnea
- Sleep apnea
- Chest pain
- Difficulty breathing
- Cough
- Chronic bronchitis
- Vocal cord dysfunction
- Throat irritation
- Hoarseness
- Chest tightness
- Wheezing
- Heartburn
- Decreased exercise tolerance.

Not all of the patients experienced all of the symptoms noted, but it can be reliably stated that all sustained respiratory injury.

34.5.4 Tungsten Carbide and Cobalt

Tungsten carbide NPs are used to produce extreme hardness and wear resistance in hard metals. Doping of tungsten carbide with cobalt further improves toughness and strength in such materials. NP-sized particles of tungsten carbide and tungsten carbide cobalt can penetrate cultured mammalian cells. In a study carried out on human and animal cultured cells it was found that NPs of tungsten carbide alone were not acutely toxic to these cells. When the tungsten carbide was doped with cobalt, however, cytotoxicity was readily apparent in all the cell cultures tested [33]. This toxic effect of the mixture demonstrates the need to test NP mixtures before their widespread use.

34.6 Summary

Nanotoxicology is a science in its infancy. As of this writing, it is known that NPs can be taken up by the human body via inhalation, ingestion, and skin contact, that it can reach the bloodstream and ultimately affect multiple body organs. It is difficult to predict the toxicity of NPs and little testing has as yet been carried out on these materials. The combination of NPs and other chemicals has received very little attention, but the small amount of research that has been done has demonstrated that such exposures can produce unanticipated effects.

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35.1 Introduction

Children are not miniature adults. Though they are continually developing from conception to adulthood, different parts of their bodies develop at different times and they are, therefore, more susceptible to toxic attack at some stages of development than others. Children are also more susceptible to impact by toxins than adults because they breathe more air, eat more food, and drink more water in proportion to their body sizes than adults do.

Research has shown that children are exposed to toxic chemicals in utero before birth and in the home, when outdoors, and at school during their growth years. Chemicals that children are commonly exposed to in these environments include the following:

- Lead
- Pesticides
- Herbicides
- Polluted air
- Polluted water
- Secondhand tobacco smoke

Cosmetics
Carpet and furniture emissions
Paint and adhesive fumes
Chemicals added to food
Flame retardants
Endocrine-disrupting chemicals that leach from plastics into foods and drinks
Runoff and emission from toxic waste sites
Industrial chemicals that are carried home on parents' clothing from work
EMR (not strictly a chemical, see Chapter 16).

Children are more sensitive to antibiotics and other pharmaceuticals as well [1], but it is beyond the scope of this book to explore this topic.

The focus of this book is the toxic effects of chemical mixtures. The following sections address this subject as it applies specifically to children. Some of the material presented here is also present in the previous chapters, where its inclusion was indicated. It is felt that the small amount of repetition here is warranted for the sake of inclusion in this chapter.

35.2 In Utero Exposure

Exposure to toxic chemicals begins in utero, with the fetus exposed to all the chemicals that the mother has in her body. The developing fetus is particularly sensitive to toxic chemical attack. Though all systems and organs are under development during gestation, not all grow or mature at the same rate or in the same time frame. This phenomenon results in the association of developmental problems from exposures during one time in pregnancy and lack of such problems from identical exposures during other gestation periods. The association between developmental problems and toxic chemical exposures will be examined in more detail in a subsequent chapter of this book. The following effects, however, are worthy of note here:

1. A developing fetus is much smaller than an adult or even a young child. The effects of chemical exposure are, therefore, much greater for the fetus. An exposure of 10ppb of PCBs will have a negligible effect on an adult, but will impair the brain development of a fetus.
2. The fetus has an immature, porous blood–brain barrier, allowing greater exposures to the developing brain.
3. The fetus has lower levels of some chemical-binding proteins, allowing greater accessibility to target organs.
4. The developing fetus's organs are rapidly developing and are more vulnerable to toxic attack than fully developed organs.
5. In the fetus, the systems and organs that detoxify and excrete toxic chemicals are not fully developed. This leads to longer residence times and correspondingly greater toxic effects.
6. Many of the effects of toxic exposure in utero are not manifested until after birth. Such effects include the onset of autism and reproductive problems, as discussed below.

In a study commissioned by the EWG, the blood of 10 American newborn babies born in U.S. hospitals in August and September of 2004 was analyzed for 413 industrial and consumer product chemicals [2]. The analysis discovered a wide variety

Table 35.1 Classes of Compounds and Their Sources Found in EWG Newborn Babies Study

Class of Compound	Source
Mercury	Pollutant from coal-fired power plants
PAHs	Combustion of fossil fuels, tobacco smoke
Polybrominated dibenzo-dioxins and -furans	Contaminants of brominated flame retardants
Perfluorinated chemicals	Breakdown products from Teflon and fabric protectors
Organochlorine pesticides	Crop application, environmental residues, bioaccumulation
Polychlorinated dibenzo-dioxins and -furans	By-products of PVC production, incineration
PBDE	Flame retardant in foams, electronics
Polychlorinated naphthalenes	Wood preservatives, lubricating oils
PCBs	Transformers and other electrical equipments

of pollutants, including mercury, pesticides, PAHs, and PCBs. In all, 287 different chemicals were found in the newborn babies' blood, with the average baby having 200 of these at birth. A list of the classes of compounds found and their sources is given in Table 35.1.

35.2.1 Toxic Hazards of Fetal Toxicants

Of the 287 different chemicals found in the EWG study, four are particularly noteworthy for the effects they bring about in later life. These chemicals are dioxin, methylmercury, PCBs, and DDE, the metabolite of the pesticide DDT.

Dioxin exposures during fetal development have been associated with endocrine-related cancers (breast and uterine) in women. Dioxin exposure in utero has also been tied to male reproductive effects. Men who are exposed in utero to dioxin father more than twice as many girls as boys. It is also associated with infant death and birth defects.

PCB exposure in the womb is associated with lower IQ scores in children and with abnormal menstrual cycles in women.

Methylmercury exposure in utero is associated with reduced brain function and a doubling of the risk of heart attacks and other cardiovascular problems.

DDE, the long-lived metabolite of DDT, is associated with premature birth and low birth weight. Low birth weight is considered an indicator of hypertension, cardiovascular disease, and the onset of type-II diabetes later in life.

The above describes what is known about only a few of the 287 chemicals detected in the blood of newborns in the EWG study. Table 35.2 lists the health effects or body system known to be affected by the chemicals found. Many of the chemicals are associated with multiple health effects. It should be noted that EWG points out that the 287 compounds were those that were particularly tested for and that no doubt many others would have been found as well had the analysis been directed at those.

Table 35.2 Health Effect or Body System Impacted by the 287 Chemicals Found

Cancer	Cardiovascular system
Birth defects	Central nervous system
Developmental retardation	Peripheral nervous system
Male reproductive system	Vision
Female reproductive system	Hearing
Endocrine system	Skin
Immune system	Liver
Respiratory system	Kidney
Gastrointestinal system	

The full health-effect impact of the 287 toxicants found on the 10 babies tested is impossible to ascertain. The chemicals found include many lipophiles and hydrophiles and the combinations possible are almost endless. Further complicating the health picture is the continued exposure of these babies to the same and other xenobiotics as they develop. Such exposure gives rise to still more toxic mixtures.

There are no known direct studies on the toxic effects of chemical exposures on the developing fetus. It is known, however, that children of tobacco smokers (tobacco smoke is a mixture of multiple lipophiles and hydrophiles) have unusually high incidences of ADHD, autism, and other developmental disorders.

It is also known that there is an association between exposure to PBDE ether flame retardants and fecundability in women. A study of Mexican-immigrant women in California showed that those with high blood concentrations of PBDE took a significantly longer period to become pregnant than controls with lower PBDE levels in their blood [3]. A recently published cohort study of more than 150 American children has shown that prenatal exposure to PBDEs results in lower neurodevelopmental test scores in exposed children than in controls [4].

It has been opined that maternal use of acetaminophen during pregnancy may be a trigger for childhood asthma by depleting glutathione in the developing lung, thereby leading to oxidative damage and inflammation. Epidemiology studies from different researchers have produced conflicting conclusions [5]. A literature review study of single-ingredient acetaminophen use on pregnant experimental animals has shown limited effects [6]. The authors of this study concluded that effects of single-ingredient acetaminophen use during pregnancy cannot necessarily be indicative of the effects to be observed when acetaminophen combination products are used. It should be noted that over-the-counter acetaminophen formulations typically contain excipient mixtures of lipophiles and hydrophiles. These include carnauba wax, powdered cellulose, hydroxyethylcellulose, and other materials. Also, acetaminophen is typically incorporated into cold and allergy formulations that contain a variety of other substances. As of this writing (2011), the relationship between maternal use of acetaminophen during pregnancy and asthma in offspring remains an open question, though as will be seen later, an association of such acetaminophen use and autism has also been suggested.

35.3 Air Pollution

As was discussed in Chapter 7, inhalation of polluted air induces respiratory disease. The sensitivity of children's developing lungs to air pollutants has been addressed in two recent studies. The first study that included 120 children in China and South Korea demonstrated that exposure to airborne particulates and polycyclic aromatic hydrocarbons produced OS in these children [7]. Increased OS has been associated with respiratory disease.

In the second study, 2497 kindergarten and first-grade children who were free of asthma and wheezing upon entering school were observed for 3 years. Traffic-related air pollution at home and at school was assessed. It was found that asthma risk increased by about 50% both near homes and near schools that were proximate to traffic-related air pollution [8]. Other asthma-related effects of pollution are discussed in Section 35.11.

35.4 Water Pollution

As has been previously noted, children drink far greater quantities of water and beverages in proportion to their body size than adults. Accordingly, toxic chemicals that pollute water are particularly dangerous to children. As has been discussed in Chapter 8, a wide variety of lipophilic and hydrophilic toxic chemicals are present in drinking water worldwide. The sources of pollution include the following:

- Farming
- Power production
- Petroleum production and refining
- Coal and metal mining
- Urban runoff
- Industrial pollution
- Home use of paints, cleaners, and other chemical products
- Pharmaceuticals released to sewer lines
- Disinfection of water
- Landfill runoff.

Many pollutants are released to surface groundwater without processing. Water so contaminated is often drawn upon for drinking purposes. Even processed drinking water often remains contaminated. Children drinking this polluted water are vulnerable to multiple toxic effects, including neurodevelopmental, liver, and kidney impacts.

35.5 Food

Toxic chemicals in food are particularly harmful to children and their developing systems. These include food additives and packaging, which contain endocrine-disrupting

chemicals, neurotoxins, and known carcinogens. The reader is referred to Chapter 10 for a complete discussion of this subject.

35.6 Chemicals in the Home

Children are exposed to numerous products in and around the home containing toxic chemicals. These include:

- Cleaners
- Air fresheners
- Disinfectants
- Wood treatments
- Paints
- Adhesives
- Fertilizers
- Pesticides.

Children very often do arts and crafts projects. In doing so they use adhesives, paints, marker pens, cleaners, and other chemical mixtures. Toxic chemicals released from such products include [9]:

- Acetone
- Acrylic monomers and oligomers
- Aliphatic and aromatic hydrocarbons
- Ammonia
- Chlorine
- Dimethyl formamide
- Dimethyl sulfoxide
- Ethanol
- Ethyl benzene
- Formaldehyde
- Isocyanates
- Isopropyl alcohol
- MEK
- Methylene chloride
- Organic peroxides
- Pigment dusts (organic and inorganic)
- 1,1,1-Trichloroethane
- Silica
- Styrene
- Toluene
- Xylene.

Exposure to these chemicals is, more times than not, to mixtures of lipophiles and hydrophiles. A more complete discussion of toxic chemicals in and around the home is presented in Chapter 11.

BFRs are compounds widely used to impart fire-retardant properties to textiles, plastics, and electronic equipment. They are incorporated into many household

products including children's pajamas, upholstery fabrics, PU foams (furniture cushion padding), construction materials, electrical equipment, and personal computers.

BFRs currently in use include:

- TBBTA
- HBCD
- PBBs
- PBDEs.

These compounds serve as flame retardants because the relatively weak carbon–bromine bonds in them are readily broken when heated. Thermal energy releases bromine radicals that couple with carbon radicals produced in fires to decrease flame sizes, thereby reducing heat and lowering carbon monoxide production [10]. They are similar in structure to PCBs and are resistant to environmental degradation.

The PBDEs are of particular concern. They are incorporated into polymer matrices, but are not covalently bonded and readily leach out of substrates holding them. These compounds are similar in structure to PCBs, are POPs, and are resistant to environmental degradation and metabolism. They can be absorbed via inhalation, ingestion, and dermal contact. The less brominated PBDE species (tetra-, penta-, and hexa-moieties) have been found in human blood, adipose tissue, and breast milk. These bioaccumulate in human adipose tissues [11].

Many PBDE mixtures are banned by the EU, but are still in use in the United States. As a result, PBDE levels in breast milk from North American mothers are at least an order of magnitude higher than those in breast milk from European women [12].

PBDEs are estrogen disruptors and neurotoxins. They are believed to cause thyroid and neurodevelopmental effects.

A more complete discussion of PBDEs is found in Section 11.6.

In addition to exposure to chemicals from products that are used in the home, children are also exposed to house dust, ingestion of which has been identified as an important source of toxic exposure to pesticides for infants and toddlers who spend considerable amounts of time playing on floors [13]. Toxic chemicals found in house dusts often include compounds which have been long banned from home use, but which remain adhered to dust particles for long periods of time.

35.7 Sick-Building Chemical Exposure

This subject is discussed in detail in Chapter 12, and the reader is encouraged to review that chapter when considering the toxicology of children.

Toxic chemicals emitted from indoor sources are particularly dangerous to young children who spend much of their time inside their homes. The sources of toxic chemicals in “sick buildings” include:

- Carpets
- Dust mites
- Stove and fireplace smoke

Wall coverings
Furniture
Textiles
Animal allergens.

35.8 Industrial Exposure

Regrettably, children living in some developing countries are employed in workshops and other settings in which they are exposed to the same industrially used chemicals as adults. Chemical exposures related to such industrial use are discussed in Chapter 13.

The children of workers in areas where those children do work in industrial settings, however, are often exposed to industrial chemicals that their parents inadvertently bring home on their clothing.

35.9 Farming: Pesticides

Children living in farming communities suffer much greater exposures to pesticides than their nonfarming cohorts due to pesticide overspray, runoff, and bonding to the clothing of their parents. A study of preschool-aged children living in agricultural communities in close proximity to fields where pesticides were applied showed impaired neurobehavioral performances similar to those observed in adults exposed to low levels of organophosphate pesticides [14].

A study of prenatal exposure to pesticides at levels that do not produce adverse effects in the mother has shown that such exposure can cause elevated blood pressure and long-lasting adverse effects on brain development in children [15]. The authors of the study concluded that pesticide exposure in utero “may contribute to a ‘silent pandemic’ of developmental neurotoxicity.”

The toxic effects of pesticide exposure are discussed in Chapter 14.

35.10 Tobacco Smoke

Tobacco smoke is very harmful to young children. Though young children do not smoke, it is estimated that more than 20 million American children are regularly exposed to secondhand smoke in the home. It is estimated that secondhand smoke is responsible for upwards of 200,000 respiratory tract infections in children under the age of 18 months and that it is the cause of more than 400 sudden infant death syndrome (SIDS) deaths annually in the United States.

Exposure to tobacco smoke from conventional cigarettes and from so-called harm-reduction cigarettes (including secondhand smoke) is toxic to children from the time of conception and throughout development. Studies have been reported that demonstrate how cigarette smoke interacts with the reproductive organs, can lead to spontaneous

miscarriage, placenta abruption, perinatal mortality, congenital malformations, decreased fecundity, decrease in birth weight and fertility rate, and affects prenatal development [16–22]. Other studies have demonstrated postnatal effects including cognition, arrested intellectual development, and behavioral and respiratory effects [23–26]. Respiratory effects are discussed in more detail in Section 35.11.

Secondhand tobacco smoke has long been associated with respiratory disease in children. The WHO has established that secondhand smoke can cause sudden death in infants [27] and it has been recently reported that children exposed to it may be at greater risk for developing atherosclerosis as adults [28].

35.11 Asthma

Children's developing respiratory systems are particularly sensitive to toxic chemical exposure and to the development of asthma. A study that followed 3677 children residing in 12 southern California communities for 8 years when the children were between 10 and 18 years of age concluded that air pollutants emanating from free-way road traffic adversely affect children's lung development. The authors concluded that such arrested lung development could result in significant deficits in lung function later in life [29].

Children exposed to polluted air containing low levels of ozone (hydrophile) and PM_{2.5} particulate matter (mixture of lipophiles and hydrophiles) are more prone to asthma than those living in areas with clean air [30].

Children who regularly swim in indoor swimming pools have been found to have higher rates of asthma than those who do not. The cause has been attributed to the reaction of disinfectant chlorine (hypochlorous acid) with organic matter (e.g., perspiration, saliva, and urine) to produce lipophilic/hydrophilic mixtures of disinfection by-products that include THMs, trihaloacetic acids, and chloramines that are inhaled by swimmers as vapors and aerosols [31].

One study has found that children and teens who smoke cigarettes have nearly 4 times the risk of developing asthma in their teens than their cohorts who do not smoke [32].

Laboratory animals exposed to disposable diaper emissions have demonstrated pulmonary irritation upon inhalation of these emissions in a test chamber [33]. Two brands of these diapers generated the following chemicals in the test chamber:

Brand 1

<i>m</i> -Xylene	3.15
<i>p</i> -Anisaldehyde	1.79
Ethylbenzene	3.15
Styrene	2.95
Cumene	3.66
Dipentene	4.57
<i>m</i> -Methoxybenzaldehyde	1.79
Methyl cinnamate	2.36.

Brand 2

Toluene 2.73

1,3,5-Trimethylbenzene 3.42

TCE 2.42

1-Methylcyclopentylamine 1.79

Dipentene 4.57.

Though exposure levels of all emissions were below their TLVs, these emission mixtures produced pulmonary irritations in mice. The results of this study suggested that disposable diaper emissions, which contain mixtures of lipophiles and hydrophiles (including hydrocarbon components that are associated with asthma development), could be a contributor to high asthma rates in countries where these types of diapers are commonly used.

WHO data demonstrate that asthma rates among children in developed countries have risen at an alarming rate [33]. Though it is generally agreed that there is a genetic component to asthma development, the high rates of asthma among children exposed to polluted air cannot be explained by genetics alone. It has become clear that the environmental factor is the overwhelming contributor to the huge increase in asthma among children exposed to air pollutants. The following studies illustrate this point.

A recently published study found a significant positive association between formaldehyde exposure and childhood asthma [34]. It should be noted, however, that references cited in that study reported conflicting results of formaldehyde-induced symptoms. A study not cited in this report noted that formaldehyde-induced respiratory effects are often reported for mixtures containing formaldehyde and that it is the mixtures that induce the effects observed [35]. It is still uncertain at this time whether or not formaldehyde alone is a trigger for asthma.

As was discussed in Section 35.2, there is inconclusive evidence linking maternal use of acetaminophen with childhood asthma [5]. Research in this area is ongoing.

35.12 Neurodevelopmental Disorders and Teratogenic Effects

Children are impacted by developmental neurotoxins and teratogens. These are manifested as autism, ADHD, and structural disorders. Autism is covered in Chapter 20, ADHD in Chapter 21, and teratogens in Chapter 24. The reader is referred to those chapters for complete discussions of the subject matter.

35.13 Children and Global Warming

As was discussed in Chapter 34, global warming is changing our planet and increasing toxic exposures for all. Children are being affected to a greater extent than adults, due to the greater vulnerability of children to toxic exposures. The increases in toxic exposure are due to changes in chemical reaction rates in air and water and changes

in air-flow patterns that affect vertical mixing of air pollutants and pollutant transport. These effects will be accelerated as the earth continues to warm.

35.14 Childhood Cancer

This subject is discussed in Chapter 36.

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36 Childhood Cancer

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36.1 Childhood Cancer

BaP is an acknowledged lung carcinogen. Exposure of mice to it results in the formation of DNA adducts in the lung. When BaP was coadministered with PCP, the PCP potentiated the effect of BaP and a significant increase in the number of DNA adducts was observed [1]. This effect, however, was observed only in adult mice and not in infant mice. The authors of the study concluded that different mechanisms are involved in the metabolism of BaP for adult versus infant mice.

The study described earlier points out significant differences between adults and children. Children are not miniature adults. They are, in many ways, far more susceptible to the carcinogenic effects of toxic chemicals than adults are, for they proportionately consume much more food and water, inhale more air, and are undergoing constant growth and continued development. When considering the effects of environmental agents on children, there is a need to take exposures during pre-conception, and those encountered during all stages of development, from in utero through the teenage years, into account [2]. This is particularly so when childhood cancers are being considered because between infancy and age 15 cancer is the leading cause of death by disease among children in the United States [3].

36.2 Prevalent Childhood Cancers

Leukemia and brain tumors are the most prevalent cancers among children aged 0–14 years in the United States. Together, they account for one half of all childhood cancers, 30% of which are leukemia and 20% of which are brain cancer [4].

Data from the SEER program (1975–1990) and the American Cancer Society show the following percentages for childhood cancer in the United States [4, 5]:

Cancer	Percentage
Leukemia	30
Glioma and meningioma	20
Neuroblastoma	8
Wilms' tumor	7
Soft tissue sarcoma	6
Non-Hodgkin's lymphoma	6
Hodgkin's disease	5
Retinoblastoma	3
Osteosarcoma	2
Ewing's sarcoma	2
Other	12

36.3 Childhood Cancer Studies

Many studies have been carried out on the effects of environmental chemical exposure and carcinogenesis in children, beginning in utero and through their teens. The following are representative of these studies where chemical mixtures were shown to be causative. Other examples will be examined in Section 36.4 on cancer clusters.

36.3.1 Tobacco Smoke

Epidemiological evidence shows that prenatal exposure to cigarette smoke, chlorinated hydrocarbons, and other organic solvents increases the incidence of cancer in offspring as carcinogens are transferred from the mother to the fetus via the placenta [6–9].

Mice prenatally exposed to cigarette smoke approximately equivalent to less than one pack of cigarettes per day demonstrated a greater than twofold increase in tumor incidence when challenged at 5 weeks of age with EL4 lymphoma cells [6].

36.3.2 Solvents

One study demonstrated that parental occupational exposures to chlorinated hydrocarbons are associated with increased risks for leukemia, lymphoma, and urinary tract cancers in offspring [8]. Another study showed associations between maternal exposures to solvents and increased incidences of leukemia. These solvents include

1,1,1-trichloroethane, toluene and other mononuclear aromatic hydrocarbons, mineral spirits, and alkanes [9].

Childhood brain cancers, the second leading cause of childhood cancer, have been associated with parental occupational exposures to toxic chemicals. Industries for which such associations have been found include [10]:

- Chemical
- Petroleum
- Electronic manufacturing
- Printing
- Graphic arts
- Metal processing
- Agriculture
- Painting.

The authors of this review study [10] point out that although frequently there are positive associations between parental occupation and childhood brain cancers, these associations are inconsistent. These inconsistencies are attributed to the use of chemicals from different sources of supply with varying additives. Put another way, the different supplies contain different chemical mixtures that may be the responsible agents.

Carcinogenic effects of environmental mixtures on children are not limited to in-utero exposures. In a study conducted on children who resided in two of the most polluted cities in the Silesia province of Poland, it was found that simultaneous exposure to PAHs and lead (emissions from coal-burning stoves) led to the induction of cytogenic effects in peripheral lymphocytes [11]. A study in Great Britain found that childhood cancers are strongly elevated by both prenatal and early postnatal exposures to oil-based combustion gases, particularly from engine exhausts [12].

The most-studied chemical mixtures that affect childhood cancer are tobacco smoke and pesticides. Childhood smoking contributes to lung and other cancers. DNA adduct formation as a consequence of tobacco smoke exposure is thought to be relevant in carcinogenesis. The younger the adolescents start smoking, the higher the levels of DNA adduct levels that are found in their systems. It is thought that smoking during adolescence produces physiological changes that lead to increased DNA adduct formation and that young smokers are more susceptible to DNA adduct formation than older people. These effects lead to higher adduct burdens than in those who start smoking later in life and thus account for the increased carcinogenesis [13].

Children's exposures to pesticides come from a wide variety of sources, including:

- Home use
- School use
- Garden use
- Pet use
- Residues in food
- Contaminated drinking water
- Agricultural application drift
- Oversprays
- Insect eradication
- Carry home from parents' occupational use.

Childhood cancers attributed to pesticide exposure include [14]:

Leukemia
Neuroblastoma
Wilms' tumor
Soft tissue sarcoma
Ewing's sarcoma
Non-Hodgkin's lymphoma
Brain
Colorectum
Testes.

36.4 Children's Cancer Clusters

Clusters of childhood cancer have been identified in several locations and suspected in others. Leukemia and brain cancer are the two most prevalent of these cancer clusters in children. The following are examples of these two types of children's cancer clusters.

36.4.1 Cluster 1: Childhood Leukemia

Woburn, Massachusetts was the location of a cluster of childhood leukemia from 1969 to 1979 [15–17]. The cluster was associated with contaminated municipal well drinking water that contained the following chemicals:

Tetrachloroethylene	3.40
1,1,2-Trichloro-1,2,2-trifluoroethane	3.09
1,1,1-Trichloroethane	2.49
TCE	2.42
<i>trans</i> -1,2-Dichloroethylene	2.09
Chloroform	1.97
PAHs	4.50–6.50
Arsenic	0.68
Chromium	0.23

Though arsenic and chromium have been associated with some cancers, none of these chemicals individually are known to be causative for leukemia.

36.4.2 Cluster 2: Childhood Leukemia

Sixteen children who lived in Fallon, Churchill County, Nevada at the time of or before becoming ill were diagnosed with leukemia between 1997 and 2002. The expected rate for the population of the county is about one in every 5 years. Toxic exposures came from several sources. They were as follows:

- The drinking water was found to contain elevated levels of uranium, arsenic, and radon.
- Surrounding fields were regularly sprayed with pesticides.
- A pipeline carrying millions of gallons of JP-8 fuel to a nearby naval base runs through the center of town and large numbers of flights have resulted in the airborne release of fuel combustion products and residues [18–22].

The chemicals that the residents were exposed to included:

Arsenic	0.68
Uranium	0.23
Radon	1.53
Carbon monoxide	1.78
Benzene	2.13
Toluene	2.73
Xylene	3.15
PAHs	4.50–6.50
Aliphatic hydrocarbons	3.50–5.00
Formaldehyde	0.35
Oxides of nitrogen	–0.60 to 0.10
1,1,1-Trichloroethane	2.49
1,4-Dichlorobenzene	3.44
Carbon tetrachloride	2.83
Ethyl benzene	3.15
Styrene	2.95
TCE	2.42
Tetrachloroethylene	3.40
Chlorpyrifos	4.96
Diethyldithiophosphate	2.24
2,4-Dichlorophenol	3.06
2,4,5-Trichlorophenol	3.72
2-Naphthol	2.70
DDE	6.51

Though benzene was found in the air samples taken, its level was far below that associated with being causative for leukemia. With the exception of naturally occurring arsenic, none of the other chemicals the children were exposed to was considered to be above acceptable levels and none was causative for leukemia.

36.4.3 Brain Cancers in Offspring of Electronic Workers

A unique cancer cluster was reported in which children of parents (both mothers and fathers) who worked at the same electronics manufacturing plant developed intracranial neoplasms [23]. Parents were exposed to some 30 different chemical classes containing more than 100 different compounds. These compounds included:

TCE	2.42
Toluene	2.73
Amyl acetate	2.26
Methylene chloride	1.25
Carbon monoxide	1.78
Nitric acid	0.21
Hydrofluoric acid	0.23
Sulfur dioxide	–2.20

Despite the large number of lipophiles and hydrophiles to which these workers were exposed, only one cancer type was reported by workers.

36.5 Summary

Children are at greater risk than adults for many cancers. Leukemia and brain cancer account for half of all childhood cancers. The causes of these cancers are often obscure, but research has shown that in-utero exposures can start the carcinogenic process that becomes fully manifest after birth. Mixtures of chemicals, most notably tobacco smoke and pesticides, are known causative childhood cancer agents. Other chemical mixtures identified as carcinogenic to children will be examined in Chapter 37 on cancer clusters.

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37 Toxicology of Global Warming

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37.1 Introduction

It was first suggested by the Swedish scientist Svante Arrhenius in 1896 that human activities which added carbon dioxide to the atmosphere could result in global warming. Ice core data show that preindustrial revolution carbon dioxide levels were 280 parts per million by volume (ppmv). By 1958, the atmospheric concentration of carbon dioxide was 316ppmv. It has risen every year since then to 387ppmv in 2008. Concentrations of carbon dioxide over the last 650,000 years have been between 180 and 300ppmv with variations of 80ppmv between the great ice ages. Thus man has, in only one century, caused changes that would have naturally taken thousands of years. Average global temperatures have risen 0.76°C and sea level has risen more than 4cm. Arctic sea ice has been dramatically reduced and almost all continental glaciers have drastically shrunk [1].

The impact of global warming on our environment is being felt in many areas. These include the following:

- Increases in airborne diseases
- Increases in waterborne diseases
- Reductions in food harvests in some areas due to rainfall pattern changes and soil erosion
- Human shelter destruction due to extreme weather conditions, tidal waves, hurricanes, and tornados washing away housing or triggering floods and landslides
- Reduced supply of usable water due to introduction of sea water into surface and subsurface aquifers

- Population migration
- Reduced sanitation and drainage
- Chemical contamination of air
- Chemical contamination of water
- Chemical contamination of soil
- Increased exposure of flora and fauna (including humans) to toxicants
- Increased disease vulnerability due to heat exposure
- Increased exposure to UV radiation due to ozone depletion
- Droughts
- Wildfires.

It is beyond the scope of this book to explore all the areas just listed and the causes for global warming. For a good introduction to the subject of human impact of global warming, the reader is referred to Refs. [2–15].

37.2 Global Warming and Human Disease

Global warming accelerates disease in humans via a number of mechanisms [11]. These include:

- Altered distribution of vector-borne factors such as mosquitoes that carry malaria
- Altered distribution of allergy-inducing pollen
- Increased toxic algal blooms
- Increase in heat stress and weakened people, making other biological or chemical attacks more severe
- Increase in diseases that cause diarrhea
- Impact on food supply
- Impact on forests.

Diseases linked to global warming include [1, 16, 17]:

- Malaria and other mosquito-borne viruses
- Dengue
- Lyme disease and other tick-borne diseases
- Leishmaniasis
- Schistosomiasis
- Chagas' disease
- Waterborne infectious diseases
- Leptospirosis, hantavirus, and other rodent-borne diseases
- Meningitis.

With the warming of the earth, and the accompanying increase in the number and intensity of storms, airborne pollen distribution will increase with adverse respiratory effects on many [18]. Increased levels of atmospheric carbon dioxide also accelerate the growth of allergy-inducing plants such as poison ivy [19].

Global warming has produced warmer waters that result in increases in algal blooms. These blooms can result in respiratory irritation and other deleterious effects [20]. It is well known that algal blooms are accelerated by increases in nutrient

availability from agricultural storm sewer runoff. These blooms are also promoted by desert dust that travels increasing distances due to more intense storms that result from global warming. The blooming of the marine biotoxin domoic acid (also known as amnesic shellfish poison) is an example of such an effect [21].

The effects of global warming on food supply, forests, and ecosystems are beyond the scope of this book and the reader is referred to the literature for further study of these areas.

Heat stress intensifies the effects of toxic chemical attacks on humans. This is explored in Section 37.6.

37.3 Extreme Climatic Events

The scientific community almost unanimously agrees that global warming is accompanied by changes in the frequency and intensity of extreme climatic events such as intense hurricanes, tornadoes, and flooding from more frequent and intense rainfall [22–24]. These events almost always result in the release of large quantities of toxic chemical mixtures of unpredictable composition. The following sections demonstrate this phenomenon.

37.3.1 *Hurricanes*

Atlantic and Pacific Ocean tropical storm and hurricane activity is monitored very closely. Starting around 1970, Atlantic Ocean hurricane frequency and intensity have increased, as have the extreme wave heights that have accompanied these storms [22, 25]. The higher wind speeds, storm surges, and greater quantities of rainfall of more intense storms result in the release of toxic chemicals into the environment from storage facilities, manufacturing plants, refineries, destroyed buildings, and impacted toxic waste sites. In the Gulf Coast region of the United States alone, hundreds of industrial chemical facilities, hazardous waste storage areas, and 56 toxic waste Superfund sites were impacted as a result of hurricanes Katrina, Rita, and Ike [22]. The chemicals released included [26]:

- Oils
- Gasoline
- Asbestos
- Lead
- Arsenic
- Chromium
- Benzene
- Naphthalene
- PAHs
- DDE
- Ethyl benzene.

Hurricane Ike made landfall in Texas in September of 2008 and hit a region containing more than 200 facilities using toxic chemicals, including two Superfund sites. Investigations revealed that 228 different sites were potentially impacted

by toxic chemicals. The sludge removed from affected homes included lead, asbestos and gasoline, and other organic chemicals [27]. A total of 18,000 containers of toxic chemicals were found to have been dislodged by storm from where they were stored.

37.3.2 Tornadoes

Tornadoes, like hurricanes, have impacted Superfund sites in the United States and have resulted in the release of mixtures of toxic chemicals.

A tornado that struck Oklahoma on May 10, 2008, swept across the mining town of Picher and hit massive piles of mining waste, releasing lead, zinc, and other heavy metals [28].

On May 25, 2008, a severe tornado hit Parkersburg, New Hartford, and Dunkerton, Iowa. Drums of toxic waste were dispersed by the tornado, and three Superfund toxic waste sites were impacted, resulting in the release of toxic chemical mixtures [29].

37.3.3 Flooding of Superfund Sites

Severe flooding following rainstorms is increasing in many geographical areas due to global warming. In the United States, such flooding has impacted Superfund sites and resulted in the release of toxic chemical mixtures. Two such areas, one in Idaho and the other in Arkansas, are illustrative of this phenomenon.

In 1997, a severe flood at Milo Creek, Idaho, washed toxic mining wastes from a Superfund site onto 50 homes. Numerous heavy metals including arsenic, cadmium, and lead flooded these homes [30].

In 1980, a flooded Superfund site at 15 Mile Bayou, Arkansas, released 500,000 gallons of waste motor oil, PCBs, and a number of heavy metals onto homes and farmland [31].

The unpredictable nature of the mixtures described in the preceding three sections makes them particularly dangerous.

Global warming is also accompanied by longer and more intense heat waves, which also have toxic implications. These are dealt with in Section 37.6.

37.4 Air Pollution

Air pollutants resulting from anthropogenic activities, including ozone, oxides of nitrogen (NO_x), PM, sulfur oxides, and organic carbon (including VOCs and PAHs) have been linked to increased asthma, other respiratory diseases, and allergic disease (Ref. [32] and numerous references contained therein). These effects have been reported for the individual components of polluted air as well as for mixtures of different components. Indeed, the increased concentrations of the various components of air pollution are intertwined.

Releases of carbon dioxide, methane, and other chemicals warm the earth and its atmosphere via the well-known greenhouse effect. The following effects result:

1. Atmospheric reaction rates are accelerated by warmer temperatures.
2. Tropospheric ozone is produced by the photo-oxidation of carbon monoxide, methane, non-methane hydrocarbons, and other VOCs in the presence of oxides of nitrogen [33].
3. Photochemical reaction rates are increased by increased intensity of UV radiation, which is in turn caused by depletion of stratospheric ozone due to the release of fluorocarbons and other man-made chemicals [34].
4. Ozone exposure is known to exacerbate asthma and cause new-onset asthma [32].

Oxides of nitrogen are produced from the atmospheric reaction of nitrogen (produced from the high temperature burning of gasoline, diesel, and other fuels) with oxygen [35]. Oxides of nitrogen are respiratory irritants and are associated with chronic and acute changes in lung function [32].

Atmospheric sulfur oxides (sulfur dioxide and sulfur trioxide) primarily come from the combustion of sulfur-containing coal [36]. Inhalation of sulfur dioxide rapidly causes the onset of bronchospastic effects after exposure [32].

Particulates, which are primarily produced by gasoline and diesel-burning vehicles, have been associated with decreased lung function in both children and adults and the worsening of asthma [37]. PM is a complex mixture of organic and inorganic components, including: metals (iron, nickel, copper, vanadium, selenium, and zinc), sulfates, VOCs such as benzene, toluene, xylene, and ethyl benzene, PAHs, and pollen [38]. PM can remain suspended in the atmosphere for long periods of time and can be wind blown thousands of miles before falling to earth [39].

Chemical pollutants can interact with pollen to exacerbate toxic effects. The combination of higher ambient temperature and increased carbon dioxide concentration speeds flower development and produces longer pollen seasons in allergenic plants. This results in dramatic increases of airborne pollen, which can interact with chemical PM to produce enhanced toxic effects on humans [32].

Global warming increases the frequency and size of wildfires. Wildfire smoke contains large quantities of carbon monoxide, carbon dioxide, oxides of nitrogen, PAHs, PM, and VOCs [40, 41]. Fires that burn in human populated areas also contain products of plastics and pesticides combustion which add to the air pollution [42].

Anthropomorphic activities have resulted in the release of numerous toxic chemicals into the environment. EPA has listed 187 of these hazardous air pollutants. The airborne concentrations of many if not all of these chemicals are increased as a result of global warming. Table 37.1 contains a list of the air pollutants characterized as hazardous by EPA [43].

Many of the compounds in Table 37.1 are naturally occurring. It is the elevated quantities found in polluted air that make them toxic. Others are man made and are toxic at very low levels. Though the introduction of these and other chemicals into the atmosphere is not necessarily due to global warming, higher ground temperatures that are due to global warming are responsible for the greater evaporation rates and higher airborne concentrations. The stronger winds due to global warming carry airborne pollutants further and many of these chemicals are now found in areas where they were not released [44].

Global warming is responsible for the release of greater quantities of toxic chemicals into the air, while depletion of the stratospheric ozone layer results in greater penetration of UV radiation into the troposphere. Together, these effects result in atmospheric chemical reactions which produce toxic chemicals not released at ground level. Almost all the organic compounds listed in Table 37.1 produce free radicals when exposed to UV radiation. These free radicals can react with other labile compounds to produce new chemicals.

It should be noted that a very large number of mixtures of unknown composition are possible from the compounds listed in this table.

37.5 Water Pollution

Higher global temperatures are raising sea level by expanding ocean water, melting glaciers and ice caps, and causing parts of the Greenland and Antarctic ice sheets to melt. EPA states: "Rising sea levels inundate wetlands and other low-lying lands, erode beaches, intensify flooding and increase the salinity of rivers, bays and groundwater tables" [45].

Rising sea level results in saltwater infusion that increases the salinity of both surface water and groundwater. Rising sea level pushes additional ocean water into estuaries and rivers, thereby presenting a risk to organisms that do not tolerate high salinity and impacting drinking water that is drawn from rivers. Shallow aquifers such as those in the Everglades in Florida and aquifers such as the one in New Jersey, east of Philadelphia, which is recharged by water from the Delaware river, are currently threatened by increasing salinity [45].

Higher water temperatures result in the dissolving of additional quantities of heavy metals and other toxicants. An example of this is the solution of greater amounts of arsenic at higher temperatures than at lower temperatures when contaminated soil is flooded [46].

Dissolved organic carbon (DOC) in water is also impacted by global warming. During the past 30 years, concentrations of DOC in lakes and streams in Europe and North America have increased. The increases are associated with global warming: increased atmospheric carbon dioxide levels and other factors [47].

The increased frequency of storms due to global warming has resulted in the contamination of surface water and groundwater from industrial effluents, municipal sewage, urban storm water runoff, and agricultural runoff [48, 49]. As a result, water sources used for human consumption have become more contaminated with heavy metals, POPs, pesticides, fertilizers, chlorination by-products, and pharmaceuticals [48].

In addition to the dangers posed from such chemical pollutants, increasing water temperatures result in increases in bacterial and parasitic populations, posing further risks to animals, humans, and ecosystems [50, 51]. Increased acidification of the oceans due to increases in atmospheric carbon dioxide has resulted in declining populations of shellfish and reduction of coral reef size [52]. Higher water temperatures have negatively impacted the estrogenic response of fish [53].

As discussed earlier, catastrophic storms are fueled by global warming. Such storms can result in the release of large quantities of toxic chemicals. In August and

Table 37.1 EPA Hazardous Air Pollutants List

Organics	
Acetaldehyde	Formaldehyde
Acetamide	Glycol ethers
Acetonitrile	Heptachlor
Acetophenone	HCB
2-Acetylaminofluorene	Hexachlorobutadiene
Acrolein	Hexachlorocyclopentadiene
Acrylamide	Hexachloroethane
Acrylic acid	Hexamethylene-1,6-diisocyanate
Acrylonitrile	Hexamethylphosphoramide
Allyl chloride	Hexane
4-Aminobiphenyl	Hydrazine
Aniline	Hydrochloric acid
<i>o</i> -Anisidine	Hydrofluoric acid
Asbestos	Hydrogen sulfide
Benzene	Hydroquinone
Benzidine	Isophorone
Benzotrichloride	Lindane
Benzyl chloride	Maleic anhydride
Biphenyl	Methanol
Bis(2-chloroethyl)ether	Methoxychlor
Bis(chloromethyl)ether	Methyl bromide
Bis(2-ethylhexyl)phthalate	Methyl chloride
Bromoform	Methyl chloroform
1,3-Butadiene	MEK
Calcium cyanamide	Methyl isocyanate
Caprolactum	Methyl methacrylate
Captan	Methyl <i>tert</i> -butyl ether
Carbaryl	4,4-Methylene bis(2-chloroaniline)
Carbon disulfide	Methylene chloride
Catechol	Methylene diphenyl diisocyanate
Chloramben	4,4'-Methylenedianiline
Chlordane	Naphthalene
Chlorine	Nitrobenzene
Chloroacetic acid	4-Nitrobiphenyl
2-Chloroacetophenone	4-Nitrophenol
Chlorobenzene	2-Nitropropane
Chlorobenzilate	<i>N</i> -Nitroso- <i>N</i> -methylurea
Chloroform	<i>N</i> -Nitrosodimethylamine
Chloromethyl methyl ether	<i>N</i> -Nitrosomorpholine
Chloroprene	PAHs
Cresols/cresylic acid	Parathion
<i>o</i> -Cresol	Pentachloronitrobenzene
<i>m</i> -Cresol	PCP
<i>p</i> -Cresol	Phenol
Cumene	<i>p</i> -Phenylenediamine

(Continued)

Table 37.1 (Continued)

2,4-D, salts and esters	Propoxur
DDE	Propylene dichloride
Diazomethane	1,2-Propyleneimine
Dibenzofurans	Quinoline
1,2-Dibromo-3-chloropropane	Quinone styrene
Dibutylphthalate	Styrene oxide
1,4-Dichlorobenzene	TCDD
3,3-Dichlorobenzidine	1,1,2,2-Tetrachloroethane
1,3-Dichloropropene	Tetrachloroethylene
Dichlorvos	Titanium tetrachloride
Diethanolamine	Toluene
<i>N,N</i> -Dimethylaniline	2,4-Toluene diamine
Diethyl sulfate	TDI
3,3-Dimethoxybenzidine	<i>o</i> -Toluidine
Dimethyl aminobenzene	Toxaphene
3,3'-Dimethylbenzidine	1,2,4-Trichlorobenzene
Dimethyl carbomyl chloride	1,1,2-Trichloroethane
DMF	TCE
1,1-Dimethylhydrazine	2,4,5-Trichlorophenol
Dimethyl phthalate	2,4,6-Trichlorophenol
Dimethyl sulfate	Triethylamine
4,6-Dinitro- <i>o</i> -cresol and salts	Trifuralin
2,4-Dinitrophenol	2,2,4-Trimethylpentane
2,4-Dinitrotoluene	Vinyl acetate
1,4-Dioxane	Vinyl bromide
1,2-Diphenylhydrazine	VC
Epichlorohydrin	Vinylidene chloride
1,2-Epoxybutane	<i>o</i> -Xylene
Ethyl acrylate	<i>m</i> -Xylene
Ethyl benzene	<i>p</i> -Xylene
Ethyl carbamate	Xylene isomer mixtures
Ethyl chloride	Inorganics
Ethylene dibromide	Antimony compounds
Ethylene dichloride	Arsenic compounds
Ethylene glycol	Beryllium compounds
Ethylene imine	Cadmium compounds
Ethylene oxide	Chromium compounds
Ethylene thiourea	Cobalt compounds
Ethylidene dichloride	Coke oven emissions
Phosgene	Cyanide compounds
Phosphine	Lead compounds
Phosphorus	Manganese compounds
Phthalic anhydride	Mercury compounds
PCBs	Fine mineral fibers
3-Propane sultone	Nickel compounds
β -Propiolactone	Radionuclides
Propionaldehyde	Selenium compounds

September of 2005, hurricanes Katrina and Rita slammed into the Gulf Coast of the United States. The U.S. EPA considers hurricane Katrina to be the largest disaster it has ever faced, with more than 200 onshore releases of hazardous chemicals and petroleum components reported. Toxic chemicals released into the water and water-body sediment and soils as a result of these storms include [54–57]:

Arsenic
Cadmium
Chromium
Copper
Iron
Lead
Manganese
Vanadium
Oils
Gasoline
Diesel fuel
Bunker fuel
POPs
VOCs.

As a result of global warming, the world is facing an almost universal degradation of drinking water quality, with 80% of the world's population and 65% of the world's river habitats affected [58, 59].

In the Arctic, global warming has had numerous effects. These include:

- Changed sea-level atmospheric pressure and wind fields
- Sea-ice drift
- Ice cover reduction
- Increased length of the melt season
- Altered precipitation patterns
- Altered hydrology
- Ocean current change
- Changed water-mass distribution
- Reduction of ice cover
- Permafrost degradation.

These changes are believed to have altered the carbon cycle and impacted biological systems. They are believed to impact the uptake of heavy metals, pesticides, and other POPs by aquatic animals. An excellent treatment of this subject has been written by MacDonald et al. [44].

37.6 Toxic Chemicals and Thermal Stress

As previously discussed, the earth is warming as a result of anthropogenic activities. Higher temperatures increase the uptake of toxic chemicals that are inhaled or that come into contact with skin. Hot environments increase pulmonary ventilation and also increase skin permeability, thereby increasing the quantities of toxic chemicals being absorbed [60–62].

Global warming also increases OS in humans. Both air pollution and thermal stress increase OS. When applied together, as is increasingly the case as the globe warms and the air becomes more polluted, they magnify the effects of OS, including neurodegenerative disorders and carcinogenesis (as discussed in Section 4.9) [63].

A recently published study has shown that exposure to cadmium and elevated temperature can also have an evolutionary effect. When *Daphnia magna* (a freshwater flea commonly used for testing ecotoxicity) were exposed to a combination of higher temperature and cadmium, microevolutionary effects (several fitness traits) were observed [64]. This research suggests that long-term exposures to thermal stress, coupled with toxic exposure, may have unanticipated evolutionary effects.

37.7 Summary

Global warming is increasing the quantity of toxic chemicals in the environment, affecting the environmental distribution of toxic chemicals, enhancing their toxicities, and adversely affecting ever greater numbers of people. Warmer water temperatures may alter the biotransformation of toxicants into more reactive metabolites and impair homeostasis. Global warming is also resulting in diminished soil quality and promoting increased insect populations, conditions that dictate that greater quantities of fertilizers and pesticides be used to produce food [65]. More highly contaminated drinking water requires the use of greater quantities of disinfectants, which in turn results in the formation of elevated quantities of toxic DBPs (see Section 8.9.2).

Finally, it should be noted that global warming is affecting and will profoundly affect children who are more vulnerable to toxic chemical attack [66–68].

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Part IV

Regulatory Requirements, Conclusions

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38 Regulatory Requirements

Chapter Outline

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38.1 Introduction

Regulatory requirements the world over dictate that hazardous chemicals and chemical products carry warning labels on them that convey health hazard information about such chemicals and products. Well-communicated warnings are instrumental in saving lives and protecting the health of people who use or are incidentally exposed to hazardous chemicals. Chemical product warnings that fail to warn, on the other hand, are often responsible for serious injuries and even death.

38.2 Warning Requirements

Chemical product warnings are often dictated by multiple governmental agencies with different responsibilities. In the United States, for example, five different federal agencies and one state agency establish the regulations that apply to chemical products. These agencies and their areas of applicability are:

1. The Occupational Safety and Health Administration (OSHA) mandates that warning labels be affixed to product containers and that MSDS be distributed to users of commercial and industrial chemicals [1].
2. The Department of Transportation (DOT) dictates warnings to be applied to shipments of chemicals [2].
3. The Consumer Product Safety Commission (CPSC) establishes regulations to enforce the Federal Hazardous Substances Act (FHSA), which requires chemical product warning labels on consumer products [3, 4].

4. The Food and Drug Administration (FDA) mandates warnings on labels for foods, personal care, and cosmetic products [5]. These are specifically exempt from regulation by other federal government agencies.
5. The Environmental Protection Agency (EPA) mandates warnings for pesticides [6]. These are also specifically exempt from regulation by other federal government agencies.

In addition to these regulations, the State of California requires that warning labels inform users if any chemical in the product is known to cause cancer or be a developmental and reproductive toxicant [7]. California also has a cosmetics disclosure law that requires the disclosure of all toxic chemicals contained in cosmetics and personal care products [8].

Canada [9], the European Union [10, 11], Australia [12], New Zealand [13], Japan [14], and the United Nations [15] (whose regulatory recommendations have been adopted by many nations) all have established chemical product warning requirements similar to those in the United States, though perhaps administered somewhat differently.

38.3 Warning Deficiencies

Most warnings that are currently (2007) applicable suffer from some deficiencies. These include:

1. The underlying toxicology used as the basis for warnings is based on the effects on healthy adults. The effects on children or on those with pre-existing medical conditions are largely ignored.
2. The warnings largely ignore the effects of mixtures. Warning information is supplied almost exclusively for the individual chemicals only.
3. The effects of “hidden” chemicals are excluded. Many of the regulations allow for proprietary formulation information to be excluded. So called “inert” ingredients are not required to be listed for proprietary purposes, even though these are added, for example, to increase activity of pesticides or improve the esthetics of cosmetics and personal care products, and are known to alter the toxicological effects of such products. In the United States, toxic chemicals in foods are not required to be listed if they are contained on the EAFUS and GRAS lists [16].
4. In the United States identification of toxic chemicals in products is only required to be listed if they are present in concentrations of 1.0% or more (or 0.1% or more, if carcinogenic). Accordingly, plastic products that are often used in surgery and in baby formula bottles are not required to warn that they contain endocrine-disrupting chemicals, which are hazardous at concentrations far less than 1% (see Section 22.2).
5. Long-term testing is not required prior to dissemination warnings. Only short-term laboratory animal tests are frequently carried out.
6. Warning language is often ambiguous. For example, the phrase, “Use With Adequate Ventilation” is found on many chemical products containing volatile components. The word *adequate* has different meanings to different people. Many warnings do not define or describe what that word means. It is implied that ventilation should be to the point where the toxic chemical is diluted to where it is no longer toxic, but no information on what that point is or how the user will know when it is reached is given.
7. To date (beginning of 2011) there are no national indoor air standards for toxic chemicals in North America, Europe, or Asia.

8. Warnings for toxic chemicals that do exist do not address children's exposures despite the fact that children absorb significantly greater quantities of toxins than adults (see Chapter 35).
9. There are no toxic chemical warning standards for students' exposures. School and University teachers are employees of their institutions and are covered in the United States by the OSHA standards, but these standards do not apply to students. Toxic chemicals that are sold to consumers in the United States have warning standards that are regulated by the CPSC, but students are not consumers.
10. None of the warning standards that are used anywhere address the combined effects of toxic exposure and heat, though the effects of toxic chemical exposure are significantly increased at higher temperatures.

38.4 Warnings for Multiple Exposures

Current regulatory requirements and chemical product warnings, for the most part, pertain to the single chemicals in the product being addressed. There are no requirements for the consideration of the context in which the product can be reasonably expected to be used and the multiple exposures that may ensue. Benzene use provides an example.

The current allowable airborne exposure level for benzene as an impurity in solvent mixtures is 0.1%. Benzene is also readily absorbed through the skin and those having dermal contact with solvents used for cleaning that contain 0.1% benzene contamination (the current allowable level) can be subjected to significant benzene absorption. In a study of workers who cleaned their hands with such solvents, the risk for leukemia was increased by 42% [17]. This example points out the need for a more stringent regulation for the allowable concentration of benzene in solvent mixtures. The authors of the cited study recommend that the allowable level be reduced from 0.1% to 0.01%. Other studies have made similar recommendations [18].

It should be noted that workers exposed to benzene by dermal contact may also inhale vapors and thus receive a dual exposure. The air in many polluted areas often contains significant benzene levels as a result of the combustion of petroleum fuels. The ambient air over Los Angeles, California, in the decade of 1990–2000, for example, typically contained greater than 1.0 ppm benzene [19]. Tobacco smokers and those exposed to secondhand (or environmental) smoke are further exposed to benzene. It is reasonable to anticipate that benzene-containing solvents will be used in urban and industrial areas where the air is polluted with benzene and that smokers will be among those who use such solvents. Such conditions further dictate the need for lowering of the allowable benzene concentration in solvents.

38.5 Warnings for Mixtures

Mixtures, having been shown to produce unanticipated effects upon exposure, require particular warning attention. Clearly, it is impossible to anticipate all the

mixtures that will be formed when a single chemical is distributed. However, it is possible to reasonably anticipate many of these. For example, ketones potentiate the neurotoxic effects of hexane [20]. These solvents are commonly mixed together in adhesives. A proper warning for a ketone, for hexane, or for an adhesive containing both of these solvents would include what is known about the potentiating effect.

Many products are mixtures. Where the combined effects of the components of the mixture are unknown, a complete list of all compounds contained in the product would enable one to decide whether or not to risk exposure to a cleaner, for example, that contains multiple lipophilic and hydrophilic species.

38.6 Odor

Warnings for chemical exposures generally address toxic effects and symptoms of exposure, with symptoms often serving as good biological indicators of overexposure and the need to cease exposure. For example, neurotoxic symptoms, such as headache, tingling, or nausea, are indicative of overexposure to CNS toxins. Odor, another biological indicator, is not always indicative of overexposure to single chemicals, since the odor thresholds for most chemicals are far below their safe exposure levels. Odor, however, may be a very valuable indicator for overexposure to mixtures of volatile compounds since most chemical exposures are to mixtures and mixture effects have been shown to frequently be present at concentrations below those of the individual components. Accordingly, odor can, in many instances, serve as a warning of toxicity of chemical mixtures. In the instance where the air odor threshold (AOT) is higher than the PEL, e.g., acetonitrile, the appearance of an odor is indicative of airborne concentrations at dangerous levels and action to reduce these concentrations is required. Table 38.1 lists current PELs [21] and AOTs [22] for a number of VOCs. All data are in parts per million (ppm).

Often, biological odors are mixed with and overwhelm chemical odors, as with discharges from landfills. Here too, odor should serve as a warning to vacate the impacted area and ventilate it. As a rule, it is recommended that the presence of an odor should serve as a warning that one is in a toxic atmosphere and should take defensive actions.

38.7 Warning Recommendations

Most environmental illnesses can be prevented by limiting exposure to toxic chemicals. Appropriately labeling chemicals and chemical products of the dangers they pose can reduce environmental toxic chemical exposures. The following recommendations are made to accomplish this goal:

1. All products containing toxic chemicals be required to list all the chemical compounds contained in them.
2. All known toxic effects of the chemicals contained in these products should be given.

Table 38.1 Permissible Exposure Levels (PEL) and Air Odor Thresholds (AOT) in ppm for VOCs [21, 22]

Chemical	PEL	AOT
Acetaldehyde	200	0.05
Acetic acid	10	0.48
Acetic anhydride	5	0.13
Acetone	250	13
Acetonitrile	20	170
Acrolein	0.1	0.16
Acrylonitrile	1	17
Allyl alcohol	2	1.1
Allyl chloride	1	1.2
Ammonia	25	5.2
<i>n</i> -Amyl acetate	100	0.054
<i>sec</i> -Amyl acetate	125	0.002
Aniline	5	1.1
Arsene	0.002	0.50
Benzene	0.1	12
Benzyl chloride	1	0.044
Bromine	0.1	0.051
Bromoform	0.5	1.3
2-Butoxyethanol	5	0.1
<i>n</i> -Butyl acetate	150	0.39
<i>n</i> -Butyl acrylate	10	0.035
<i>n</i> -Butyl alcohol	50	0.83
<i>tert</i> -Butyl alcohol	200	47
<i>n</i> -Butyl amine	5	1.8
Camphor	2	0.27
Carbon disulfide	1	0.11
Carbon tetrachloride	2	96
Chlorine	0.5	0.31
Chlorobenzene	75	0.68
Chloroform	10	85
<i>m</i> -Cresol	2.3	0.00028
Cumene	50	0.088
Cyclohexane	300	25
Cyclohexanol	50	0.15
Cyclohexanone	25	0.88
Cyclopentadiene	75	1.9
<i>p</i> -Dichlorobenzene	75	0.18
<i>trans</i> -1,2-Dichloroethylene	100	17
Diethanolamine	10	0.011
Diethylamine	10	0.13
Diethyl ketone		200
Diisobutyl ketone	25	0.11

(Continued)

Table 38.1 (Continued)

Chemical	PEL	AOT
Dimethylamine	10	0.34
1,4-Dioxane	1	24
Epichlorohydrin	5	0.93
Ethanolamine	3	2.6
2-Ethoxyethanol	0.5	2.7
Ethyl acetate	400	3.9
Ethyl acrylate	5	0.0012
Ethyl alcohol	1000	84
Ethyl amine	10	0.95
Ethyl benzene	100	2.3
Ethyl chloride	1000	0.95
Ethyl formate	0	31
Fluorine	0.1	0.14
Formaldehyde	0.1	0.83
Formic acid	5	49
Hydrazine	0.03	3.7
Hydrogen bromide	3	2
Hydrogen chloride	5	0.77
Hydrogen cyanide	10	0.58
Hydrogen fluoride	3	0.042
Isoamyl acetate	250	0.025
Isoamyl alcohol	100	0.042
Isobutyl acetate	150	0.64
Isobutyl alcohol	150	1.6
Isopropyl acetate	250	2.7
Isopropyl alcohol	400	22
Isopropyl amine	5	1.2
Maleic anhydride	0.25	0.32
Methyl acrylate	10	0.0048
Methyl alcohol	200	100
Methyl amine	10	3.2
Methylene chloride	25	250
MEK	200	5.41
Methyl isopropyl ketone	200	1.9
Methyl methacrylate	100	0.083
Napthalene	10	0.084
Nitrobenzene	1	0.018
Nitrogen dioxide	1	0.39
<i>m</i> -Nitrotoluene	2	0.045
Phosgene	0.1	0.9
Phthalic anhydride	1	0.053
Propylene glycol 1-methyl ether	100	10
Tetrachloroethylene	50	27
Tetrahydrofuran	200	2.0

(Continued)

Table 38.1 (Continued)

Chemical	PEL	AOT
Toluene	100	2.9
<i>o</i> -Toluidine	2	0.25
TCE	350	120
TCE	50	28
Trimethyl amine	10	0.00044
Vinyl acetate	4	0.5
VC	1	3000
Vinylidene chloride	1	190
Xylene	100	1.1

3. Information about the toxicity of mixtures contained in each product along with the reasonably anticipated mixtures that will be formed from the use of the chemicals in the products should be included in the warnings.
4. PEL and MCL levels for all chemicals be reduced by at least a power of 10 to account for mixture effects which are frequently manifested at concentrations that are lower than those at which the individual chemicals induce effects.
5. Regulatory authorities be established initially in each country and subsequently worldwide to review and approve chemical product warning labels to assure that the best available knowledge about toxicity is universally distributed. This authority could be similar to that exercised by EPA in the United States in reviewing and approving pesticide product labels [6].
6. Review and approval of warning labels be required prior to the release of a chemical product into the stream of commerce.
7. A universal registry be established to catalog and make available information about the toxic effects of single chemicals and mixtures as these become known. This registry could be similar to those for pharmaceuticals that are kept by the FDA in the United States [5].
8. Permanent ongoing review of warnings be required to incorporate new findings into them. This could be accomplished via automatic notification of manufacturers and distributors of chemical products with approved labels by the regulatory body when new information becomes available. Such notification should automatically be conveyed to medical practitioners including hospital emergency rooms.
9. All chemical products contain current toxicological information, a list of symptoms that would be indicative of overexposure and directions for actions to take upon exposure.
10. All volatile chemicals and chemical products carry a warning to take protective action if the user smells a chemical odor or experiences other biological effects.
11. The combination of warning labels and MSDS be used to convey warnings.
12. School-aged students be taught to read and understand chemical product warnings in their science classes.
13. Include temperature effect warnings on industrial and consumer products.

38.8 Summary

A good warning label will scare a user into action. Warnings for toxic chemicals and chemical products currently inadequately address the hazards of chemicals and particularly chemical mixtures, which often produce toxic effects at lower concentration

levels than the individual chemicals. An informed user of chemicals will almost always be better protected than one ignorant of the dangers posed. Regulatory agencies can take steps to make sure that the public is better informed about the hazards of chemical products.

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39 Conclusions and Recommendations

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If we knew what we were doing it wouldn't be called research, would it?

Albert Einstein

39.1 Introduction

Exposure by humans to chemical mixtures produces effects that are often not predicted from the known toxicology of the individual components of the mixtures. The preceding chapters have demonstrated this for every system and organ studied. The thousands of studies examined lead to certain conclusions and recommendations. These are presented here.

39.2 Conclusions

The following conclusions can be drawn for the toxic effects of chemical mixtures:

1. Exposures to chemical mixtures containing at least one lipophilic and one hydrophilic chemical may produce greater than anticipated effects, i.e., more severe symptoms, unpredicted effects on organs not known to be affected by the individual components and/or effects at concentrations much lower than those known to be harmful for the individual chemical species (Chapter 2).
2. Concentrations of individual chemicals in a mixture are not necessarily predictive of the ultimate toxic effects (Chapter 2).
3. Lipophilic species facilitate the absorption of hydrophilic species through lipophilic membrane barriers, resulting in the uptake of greater quantities of hydrophiles than would be absorbed if the lipophiles were not present (Chapter 3).

4. Lipophile-enhanced absorption may occur through the skin, via inhalation or ingestion (Chapter 3).
5. The effects of the absorbed mixtures may be acute, chronic, or carcinogenic. In the case of carcinogenesis, the individual chemicals are often not known to be cancer causing (Chapters 32 and 33).
6. Some effects of mixtures may become predictable, particularly in simple binary mixtures. For example, carbon tetrachloride reacts synergistically with both ethanol and isopropanol as a liver toxin. Predictability is less reliable in complex mixtures that are prevalent in most environmental exposures [1].
7. The toxic effects of lipophilic:hydrophilic mixtures may not necessarily be predictive of the ultimate toxic mechanism. Such mixtures induce the toxic effects by absorbing and transporting greater quantities of toxic chemicals to their ultimate sites of action [2, 3].
8. A chemical mixture may act as a single entity in inducing toxic effects [2].
9. Mixtures of chemicals may target multiple organs, just as numerous single chemicals do (Chapter 26).
10. Mixtures may act via several different mechanisms (Chapter 4).
11. Chemical mixtures that attack multiple organs may act via a weakening of the body's natural immune system response. This is particularly the case when one component of the mixture attacks the immune system, thus weakening that system's response to an attack on another organ by a second component of the mixture (Chapter 25).
12. Many chemical mixtures produce antagonistic effects, e.g., carbon disulfide or pyridine lessen the hepatotoxicity of carbon tetrachloride [1]. As a result of such antagonisms, some have proposed that exposures to low levels of certain toxic chemicals be encouraged as protective of health [4]. Such an approach is contradicted by the overwhelming evidence of the toxic effects of mixtures and the unpredictability of how such chemicals will interact with other toxic chemicals to which an individual is exposed. In the same vein, some have encouraged the use of pesticides as protective of the food supply, arguing that naturally occurring carcinogens are more widespread than synthetic ones. The toxic and carcinogenic effects of even trace quantities of pesticides (almost always applied as mixtures with often unpredicted toxic effects), however, dictate that such an approach is dangerous and that pesticides are far more toxic once released into the environment than simple single-species studies would suggest [5].
13. It is estimated that 2 million people die prematurely each year because of air pollution [6] and that nearly one-quarter of all deaths and one-third of the deaths of children can be attributed to environmental factors [7]. Virtually all environmental exposures are to mixtures of lipophilic and hydrophilic chemicals.
14. Energy production is the primary cause of air pollution. The incomplete combustion of fuel when generating electricity, heating buildings, and powering transportation systems all contribute to air pollution [8–13].
15. More than 2.4 billion people worldwide rely on wood, charcoal, animal dung, crop wastes, and coal as indoor energy sources. These fuels combust incompletely in household stoves, producing carbon monoxide, carbon black, methane, and VOCs that have been associated with COPD, cancers, and other illnesses [8].
16. Energy production is also associated with the release of greenhouse gases that adversely affect climate change [8, 14]. The release of carbon dioxide, methane, and other greenhouse gases continue to raise ambient temperatures. Increased environmental temperatures lead to accelerated photochemical smog and aqueous pollution producing reactions with resulting health consequences from exposures to the toxic chemicals released. Examples of such effects are the increased production of ozone in warmer air and DBPs and increased

solubility of heavy metals in warmer water. Increased ambient temperatures promote insect growth, with a corresponding increase in the pressure to apply even greater quantities of pesticides [13]. Using renewable sources of energy (e.g., solar and wind energy) would greatly eliminate toxic chemical release into the environment. It is estimated that less than 2% of the land area in the United States could provide all of the country's energy from solar sources [8].

17. WHO estimates that tobacco smoke will result in the deaths of 1 billion people in the twenty-first century [15]. As was seen in the preceding chapters, tobacco smoke exposure has been shown to adversely affect virtually every human body system and it is the single largest cause of chemical injury and death in the world (Chapter 15). New deleterious effects of tobacco smoke are constantly being discovered.
18. Children are most vulnerable to the effects of toxic chemical exposure. Because they are still developing, children are affected in adverse ways that adults are not (Chapters 24, 35, and 36). For their body sizes, children inhale more air, drink more water, and eat more food than adults and are thereby exposed to correspondingly higher levels of toxic environmental chemicals. This dictates that children require greater protection from exposures to toxic chemicals and their mixtures than adults do.
19. New information is constantly forthcoming. For example, approximately 600–700 DBPs have been identified in drinking water disinfected by chlorine, ozone, chlorine dioxide, chloramines, and their combinations, with new ones being discovered all the time [16]. Such complexity demonstrates the difficulty associated with trying to ascribe the causes of environmental toxic effects when people come down with “strange” illnesses and reactions. An example is increased rates of spontaneous abortions in women who drink water with elevated levels of THMs and other DBPs (Chapters 8 and 23). The mixture possibilities in disinfected water, for example, are endless and the exact causes of toxic consequences are extremely difficult to pin down.
20. Often, different research groups find conflicting results from similar experiments. In many of these instances, exposure mixtures have not been completely defined. For example, studies with human volunteers in test chambers showed much higher tolerances to formaldehyde (a hydrophile) with respect to dyspnea symptoms than to formaldehyde when exposure was concurrent with exposure to terpenes (lipophiles) by wood workers [17, 18].
21. Warnings put on chemical products are inadequate for mixtures for they almost never address the toxic consequences of mixture exposure. Warnings also generally fail to address the greater effects on children and others that are more vulnerable than the general adult population (see Chapter 35).
22. With the passage of time, many previously unexplained diseases and injuries have been related to toxic chemical mixture exposures. These include CNS, respiratory system, immune system, carcinogenic, and other end points [19]. Further such discoveries are to be anticipated.

39.3 Recommendations

The hundreds of studies cited in this book, as well as my own ongoing research, led me to recommend the following. These recommendations are presented in no particular order.

1. Air and water pollution restrictions need to be made more stringent. Emission standards should be set at best available technology standards.

2. Under no circumstances should pollution emitters that exceed current standards be allowed to sell pollution credits that allow others to contaminate our environment and contribute to global warming. We are headed toward an environment with vastly increasing quantities of toxic pollutants and all efforts should be made to curtail the emissions of toxins.
3. The allowable levels of air and water emissions of toxic chemicals should be reduced by at least one order of magnitude to account for the toxic effects of mixtures that remain largely unknown, but are increasingly being found to induce toxic effects at very low concentration levels. Endocrine-disrupting chemicals and mixtures are examples of such compounds (Chapter 22).
4. New technology, e.g., nanotechnology, must be carefully evaluated for toxic consequences *prior* to widespread introduction (Chapter 34). In the example of nanoparticles, unanticipated toxic effects are being found as these circulate throughout the human body.
5. Education of the toxic effects of chemicals and chemical mixtures should become more widespread. Students should be taught how to read and understand warning labels and MSDS in their science classes and to avoid contact with chemicals whenever possible. Public service advertisements can be used to educate people about the need to limit toxic emissions, about the safe use of chemical products, and how to avoid unnecessary exposures.
6. Chemical mixtures that contain lipophilic and hydrophilic components should be considered harmful unless proven otherwise.
7. Chemical products should be formulated as lipophilic only or hydrophilic only where possible (e.g., as in cleaners) to limit exposures to mixtures with unknown toxic effects.
8. Foods, drinks, pharmaceuticals, and personal care products should not be packaged in plastics that contain compounds that can migrate out, such as bisphenol A and phthalates.
9. Solar energy must be harnessed so that fuel combustion for energy production (the single largest source of environmental pollution) can be largely eliminated.

39.4 The Future

The understanding of the toxic effects of chemical mixtures is in its infancy. Ongoing research, both mine and that of others, is working toward quantifying the toxic effects of chemical mixtures so that these effects may become predictable and that realistic exposure levels can be recommended. Our current knowledge has revealed only the proverbial tip of the iceberg. Einstein's quotation at the start of this chapter seemingly applies in the area of toxic effects of chemical mixtures. It is my hope that this book will stimulate the research that is needed to expand our knowledge.

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